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(57) Abstract

The present invention relates to rigid chiral ligands useful in making catalysts for asymmetric synthesis. More particularly, the present invention relates to new monodentate and bidentate cyclic chiral phosphine ligands which are formed into catalysts to provide high selectivity of the enantiometric structure of the end-product.

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Asymmetric Synthesis Catalyzed by Transition Metal Complexes with Cyclic Chiral Ligands

This application claims priority to the following U.S. provisional applications: 60/019,938 filed on June 14, 1996; 60/033,493 filed on December 20, 1996; and 60/____ filed on May 9, 1997.

Technical Field of the Invention

The present invention relates to rigid chiral ligands useful in making catalysts for asymmetric synthesis. More particularly, the present invention relates to new monodentate and bidentate cyclic chiral phosphine ligands which are formed into catalysts to provide high selectivity of the enantiomeric structure of the end-product.

Background of the Invention

The biological activities of many pharmaceuticals, fragrances, food additives and agrochemicals are often associated with their absolute molecular configuration. While one enantiomer gives a desired biological function through interactions with natural binding sites, another enantiomer usually does not have the same function and sometimes has deleterious side effects. A growing demand in pharmaceutical industries is to market a chiral drug in enantiomerically pure form. To meet this challenge, chemists have explored many approaches for acquiring enantiomerically pure compounds ranging from optical resolution and structural modification of naturally occurring chiral substances to asymmetric catalysis using synthetic chiral catalysts and enzymes. Among these methods, asymmetric catalysis is often the most efficient because a small amount of a chiral catalyst can be used to produce a large quantity of a chiral target molecule. During the last two decades, great effort has been devoted to discovering new asymmetric catalysts and more than a half-dozen commercial industrial processes have used asymmetric catalysis as the key step in the production of enantiomerically pure compounds.[1]

Asymmetric phosphine ligands have played a significant role in the development of novel transition metal catalyzed asymmetric reactions. Over 1000 chiral diphosphines[2]

have been made since the application of the DIPAMP ligand[3] for the industrial production of L-Dopa, yet only a few of these ligands afford the efficiency and selectivity required for commercial applications. Among these ligands, BINAP is one of the most frequently used bidentate chiral phosphines. The axially dissymmetric, fully aromatic BINAP ligand has been demonstrated to be highly effective for many asymmetric reactions. Duphos and related ligands have also shown high enantioselectivities in numerous reactions. However, there are a variety of reactions in which only modest enantioselectivity has been achieved with these ligands. Highly selective chiral ligands are needed to facilitate asymmetric reactions.

Figure 1 lists known chiral bidentate phosphines (DIPAMP,[3] BPPM,[4] DEGPHOS,[5] DIOP,[6] Chiraphos,[7] Skewphos,[8] BINAP,[9] Duphos,[10] and BPE[10]). While high selectivities were observed in many reactions using some of these chiral diphosphine ligands, there are many reactions where these ligands are not very efficient in terms of activity and selectivity. There are many disadvantages associated with these ligands, which hinder their applications. For DIPAMP, the phosphine chiral center is difficult to make. This ligand is only useful for asymmetric hydrogenation reaction. For BPPM, DIOP and Skewphos, the methylene group in the ligands causes conformational flexibility and enantioselectivities are moderate for many catalytic asymmetric reaction. DEGPHOS and CHIRAPHOS coordinate transition metal in five-membered ring. The chiral environment created by the phenyl groups is not close to the substrates and enantioselectivities are moderate. BINAP, DuPhos and BPE ligands are good for many asymmetric reactions. However, the rotation of aryl-aryl bond makes BINAP very flexible. The flexibility is an inherent limitation in the use of phosphine ligands. Furthermore, because the BINAP contains three aryl groups, it is less electron donating than phosphines that have less aryl groups. This is an important factor which influences reaction rates. For hydrogenation reactions, electron donating phosphines are more active. For the more electron donating DUPHOS and PBE ligands, the five membered ring adjacent to the phosphines is flexible.

U.S. Patents 5,329,015; 5,386,061; 5,532,395 describe phosphines prepared through chiral 1, 4-diols. These patents also describe divalent aryl and ferrocene bridging groups. U.S. Patent 5,258,553 describes chiral tridentate ligand phosphine ligands. The

above ligands are made into Group VIII transitional catalyst and are used to conduct enantioselective catalytic reactions such as asymmetric hydrogenation of olefins, ketones and imines. These references illustrate the preparation of catalyst from phosphine ligands and the conducting of various asymmetric synthesis. These patent disclosures are incorporated herein by reference.

The present invention discloses several new bidentate and monodentate phosphine ligands for asymmetric catalysis. The common feature of these ligands are that they contain rigid ring structures useful for restricting conformational flexibility of the ligands, thus enhancing chiral recognition. The present invention provides families of chiral diphosphines by variation of the steric and electronic environments (i.e., change of P-M-P bite angles and substituents on phosphine). In such a manner, the present invention provides an efficient and economical method with which to synthesize chiral drugs and agrochemicals.

Brief Description Of The Figures

Figure 1 list known chiral bidentate phosphines. While high selectivities were obtained in many reactions using some of these chiral diphosphine ligands, there are many reactions where these ligands are not very efficienct in terms of activity and selectivity. There are many disadvantages associated with these ligands, which hinder their applications. For DIPAMP, the phosphine chiral center is difficult to make. This ligand is only useful for limited application in asymmetric hydrogenation. For BPPM, DIOP, and Skewphos, the methylene group in the ligands causes conformational flexibility and enantioselectivities are moderate for many catalytic asymmetric reactions. DEGPHOS and CHIRAPHOS coordinate transition metals in five-membered ring. The Chiral environment created by the phenyl groups is not close to the substrates and enantionselectivities are moderate for many reactions. BINAP, DuPhos and BPE ligands are good for many asymmetric reactions. However, the rotation if aryl-aryl bond makes BINAP very flexible. The flexibility is an inherent limitation in the use of phosphine ligand. Furthermore, because the phosphine of BINAP contains adjacent three aryl groups , it is less electron donating than phosphine that have less aryl groups. This is an important factor which influences reaction rates. For hydrogenation reactions, electron

donating phosphines are more active. For the more electron donating DUPHOS and BPE ligands, the five-membered ring adjacent to the phsophines is flexible.

Figure 2 illustrates ligands 1-13 (Type I). These ligands have at less four chiral centers in their backbones and they can form seven-membered chelating ring with many transition metals. The two cyclic rings in the backbone limit the conformational flexibility. The two carbon stereogenic centers adjacent to PR_2 may be inverted as illustrated in Figure 2.

Figure 3 depicts ligands 14-23. Ligands 14-16 (Type II) have a nitrogen-phosphine bond in the ligands. Ligands 17-19 (Type III) have many phosphine-oxygen bonds. Ligands 20-23 (Type IV) have spiro-ring structure in their backbones. These ligands can be regarded as derivatives of ligands 1-13 with structure variation of their backbones.

Figure 4 depicts ligands 24-34 (Type V), chiral phosphines with phospha-tricyclic structures.

Figure 5 and 6 illustrate type VI chiral phosphines with fused phospha-bicyclic structures.

Figure 7 shows type VII chiral phosphine ligands having one or two rings in their backbones.

Figure 8 outlines the synthesis of the type I ligands, 1-13. Asymmetric hydroboration of dienes or hydroboration of chiral dienes can lead to chiral 1,4-diols. Chiral resolution of diols can also provide an effective routes to chiral diols. Dienes and chiral dienes may be generated using variety of methods including but not limited to Pinacol coupling and elimination, aldol condensation followed by reduction and elimination, Methathesis, and coupling of vinyl halide or vinyl lithium. Mesylation of diols and nucleophilic attack of mesylates with a variety of phosphides can produce the desired products. With chiral dienes, the free-radical addition of HPR_2 may lead to the products. For the inversion of the chiral diol, Mitsunobo reaction may be applied.

Figure 9 illustrates the synthesis of ligands 14-23. For the chiral ligands containing P-O or P-N bonds, the corresponding chiral diols or chiral diamines are presented. For the spiro phosphines, one pathway is to construct spiro-structure in the

last step. This is because direct nucleophilic attack by $LiPPh_2$ to the corresponding spiro dimesylate is difficult due to the steric hinderance of adjacent carbon group.

Figure 10 describes the synthesis of phospha-tricyclic compounds from the corresponding diols.

Figure 11 and 12 describes the synthesis of chiral fused phospha-bicyclic compounds. A typical procedure uses $RPLi_2$ as nucleophiles. However, phospha-bicyclic anion can be made and nucleophilic attack with bridge groups (XRX or RX where R is alkyl or aryl and X is a halide, tosylate or mesylate) by this anion can generate the desired ligands.

Figure 13 outlines the synthetic procedures for ligands 45 to 50.

Figure 14 illustrates applications of asymmetric catalytic reactions.

Summary Of The Invention

It is an objective of the present invention to provide a chiral diphosphine ligand that provides high enantioselectivity and activity. The present invention therefore provides a chiral phosphine ligand having a conformationally rigid cyclic structure, in which the phosphorus may be bonded to or be part of the cyclic structure. As such, the ligand rigidity provides enhanced chiral discrimination in metal catalyzed asymmetric organic reactions. In one embodiment, a "type I" or "type II" chiral bidentate phosphine ligand having a 2,2'-bis(diorganophosphino)-1,1'-bis(cyclic) structure wherein each cycle of the bis(cyclic) structure comprises 3 to 8 carbon atoms wherein the 1, 1', 2 and 2' carbon atoms in the bis(cyclic) structure are saturated carbon atoms and wherein the carbon atoms in the bis(cyclic) structure other than the 1, 1', 2 and 2' carbon atoms are optionally replaced with a heteroatom including but not limited to nitrogen, oxygen or sulfur; and wherein type II ligands have nitrogen in the 2,2' position, is provided.

In another embodiment, a "type III" chiral bidentate phosphine ligand having a 1,1'-bis(cyclic)-2,2'(organophosphinite) structure is provided.

In yet another embodiment, a "type IV" chiral phosphine ligand having a heteroatom-containing sprio bis-organophosphine or organophosphinite is provided.

In one embodiment, a "type V" chiral bidentate phosphine ligand having a (bis)phospha-tricyclic structure with a bridge group is provided.

In another embodiment, a "type VI" chiral phosphine ligand having a (bis)fused phospha-bicyclic structure comprising a bridge structure is provided.

In yet another embodiment, a "type VIIa" chiral phosphine ligand having a cis(bis) phosphine fused bicyclic structure is provided.

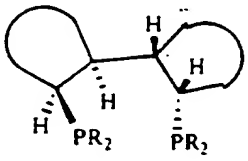
In one embodiment, a "type VIIb" chiral phosphine ligand having a cis or trans biphosphine cyclic structure having two R' substituents where R' is alkyl, fluoroalkyl or perfluoroalkyl (each having up to 8 carbon atoms), aryl, substituted aryl, arylalkyl, ring-substituted arylalkyl, and $-CR'_2(CR'_2)_qZ(CR'_2)_pR'$ where q and p are the same or different integers ranging from 1 to 8 and Z is defined as O, S, NR, PR, AsR, SbR, divalent aryl, divalent fused aryl, divalent 5-membered ring heterocyclic group, or a divalent fused heterocyclic group where R is alkyl of 1-8 carbon atoms, aryl, or substituted aryl is provided. In another embodiment, a "type VIIc" chiral phosphine ligand having a trans(bis) phosphine bicyclic structure.

In yet another embodiment, a "type V" chiral monodentate phosphine ligand comprising a phospha-tricyclic structure is provided.

And, in yet another embodiment, a "type VI" chiral monodentate phosphine ligand comprising a phospha-bicyclic structure is provided.

And, in yet another embodiment, a cyclic phosphine ligand having a structure of :

A. Bidentate cyclic chiral phosphines:



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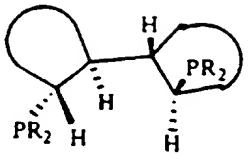

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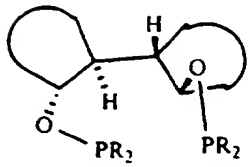

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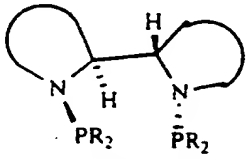

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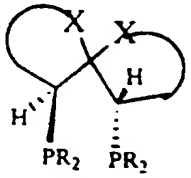

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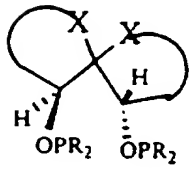

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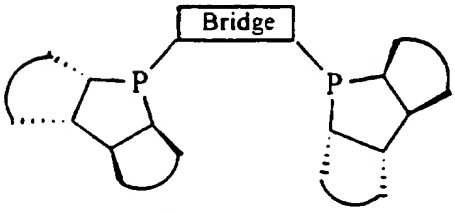
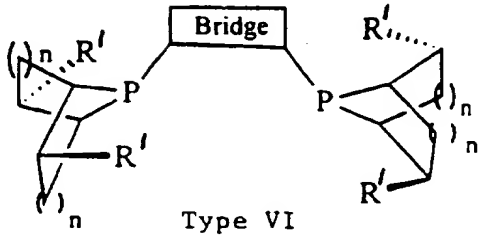
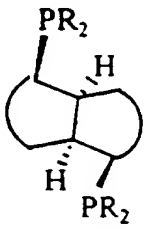


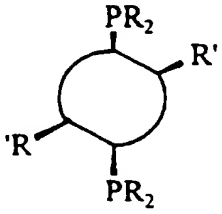
Type V



Type VI



Type VIIa



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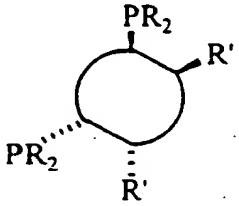

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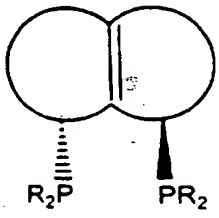
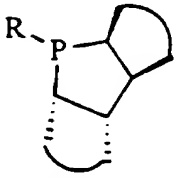


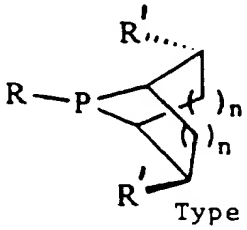
Type VIIc

or

B. monodentate cyclic chiral phosphines



Type V



Type VI

where each R is independently alkyl of 1-8 carbon atoms, substituted alkyl, aryl, or substituted aryl; each R' is independently alkyl, fluoroalkyl and perfluoroalkyl, each having up to 8 carbon atoms; aryl; substituted aryl; arylalkyl; ring-substituted arylalkyl; and $-CR'_2(CR'_2)_qZ(CR'_2)_pR'$ wherein q and p are the same or different integers ranging

from 1 to 8, R' is as defined above, and Z is selected from the group consisting of O, S, NR, PR, AsR, SbR, divalent aryl, divalent fused aryl, divalent 5-membered ring heterocyclic group, and a divalent fused heterocyclic group where R is as defined above; the cyclic structure D represents a ring having 3 to 8 carbon atoms which may be substituted within the ring with one or more oxygen, sulfur, N-R', C=O, or CR'_2; D represents 0 to 8 carbon atoms; and where the ring may further be substituted with R' as defined above; the Bridge is $-(CH_2)_r-$ where r is an integer ranging from 1 to 8; $-(CH_2)_sZ(CH_2)_m-$ wherein s and m are each the same or different integers ranging from 1 to 8; 1,2-divalent phenyl; 2,2'divalent-1,1'biphenyl; 2,2'divalent 1,2'binapthyl; and ferrocene; each of which may be substituted with R' as defined above; and where the substitution on 1,2-divalent phenyl, the ferrocene or biaryl bridge is independently hydrogen, halogen, alkyl, alkoxyl, aryl, aryloxy, nitro, amino, vinyl, substituted vinyl, alkynyl, or sulfonic acid; X is O, S or NR where R is as defined above; and n is 1 or 2.

It is yet another objective of the present invention to provide a catalyst that provides high enantioselectivity and activity; in one embodiment of the present invention, a chiral phosphine ligand as described above complexed with a transition metal, preferably rhodium, iridium, ruthenium, palladium or platinium is provided.

In certain compounds of the present invention, the phosphine ligand is attached to an organic substrate or backbone by a chemical bridging group or organic substituent. For these compounds, it is preferred that the chemical bridging group or organic substituent has a linker to a polymer. The polymer-supported catalyst is a heterogenous or homogenous catalyst, dependent upon the solubility of the polymer in the reaction medium.

It is another objective of the present invention to provide a method for transition metal complex catalyzed asymmetric hydrogenation of ketones, imines, or olefin; in one embodiment, a method is provided in which such a reaction is catalyzed by a chiral phosphine ligand as described above complexed with a transition metal, preferably rhodium, iridium, ruthenium, palladium or platinium is provided.

It is yet another objective of the present invention to provide an improved method for a transition metal catalyzed asymmetric reaction such as hydrogenation, hydride transfer reaction, hydrosilylation, hydroboration, hydrovinylation, hydroformylation,

hydrocarboxylation, allylic alkylation, cyclopropanation, Diels-Alder reaction, Aldol reaction, Heck reaction, Michael addition, and stereo-selective polymerization in one embodiment, the improvement comprising catalysing the reaction with a catalyst that is a chiral phosphine ligand as described above complexed with a transition metal, preferably rhodium, iridium, ruthenium, palladium or platinium. In yet another embodiment, the catalyst is selected from the group consisting of compound 1 as illustrated in Figure 1, compound 36 as illustrated in Figure 5, compound 40 as illustrated in Figure 6, and compound 26 as illustrated in Figure 4. In another embodiment, the catalyst is a complex of a chiral phosphine complexed with a compound that is $[Rh(COD)Cl]_2$, $[Rh(COD)_2]X$ (X = BF_4, ClO_4, SbF_6, CF_3SO_3), $[Ir(COD)Cl]_2$, $[Ir(COD)_2]X$ (X = BF_4, ClO_4, SbF_6, CF_3SO_3,), $Ru(COD)Cl_2$, $[Pd(CH_3CN)_4[BF_4]_2$, $Pd_2(dba)_3$, and $[Pd(C_3H_5)Cl]_2$. And, in yet another embodiment, the catalyst is $Ru(RCOO)_2(Y)$, $RuX_2(Y)$, $Ru(methylallyl)_2(Y)$, $Ru(aryl\ group)X_2(Y)$, where where X is Cl, Br or I and Y is a chiral diphosphine of the present invention.

It is yet another objective of the present invention to provide an improved method for asymmetric hydration of a ketone, imine or olefin catalyzed by a complex comprising Ru, Rh and Ir and a chiral ligand; in one embodiment, the improvement includes conducting the catalysis with a palladium complex having a chiral phosphine ligand as described above. In yet another embodiment, the catalyst is selected from the group consisting of compound 1 as illustrated in Figure 1, compound 36 as illustrated in Figure 5, and compound 26 as illustrated in Figure 4.

It is another method of the present invention to provide an improved method for asymmetric allyllic alkylation catalyzed by a complex comprising palladium and a chiral ligand; in one embodiment, the improvement includes catalysis with a palladium complex having a chiral ligand as described above. In yet another embodiment, the catalyst includes compound 40 as illustrated in Figure 6.

It is yet another objective of the present invention to provide an intermediate for synthesis of a chiral phosphine ligand. In one embodiment, the intermediate shown as compound 3 in Scheme 2 is provided.

NR, PR, AsR, SbR, divalent aryl, divalent fused aryl, divalent 5-membered ring heterocyclic group, and a divalent fused heterocyclic group where R is as defined above; the cyclic structure D represents a ring having 3 to 8 carbon atoms which may be substituted within the ring with one or more oxygen, sulfur, N-R', C=O, or CR'_2; ⊃ represents 0 to 8 carbon atoms; and where the ring may further be substituted with R' as defined above; the Bridge is $-(CH_2)_r-$ where r is an integer ranging from 1 to 8; $-(CH_2)_sZ(CH_2)_m-$ wherein s and m are each the same or different integers ranging from 1 to 8; 1,2-divalent phenyl; 2,2'divalent-1,1'biphenyl; 2,2'divalent 1,2'binapthyl; and ferrocene; each of which may be substituted with R' as defined above; and where the substitution on 1,2-divalent phenyl, the ferrocene or biaryl bridge is independently hydrogen, halogen, alkyl, alkoxyl, aryl, aryloxy, nitro, amino, vinyl, substituted vinyl, alkynyl, or sulfonic acid; X is O, S or NR where R is as defined above; and n is 1 or 2.

It is yet another objective of the present invention to provide a catalyst that provides high enantioselectivity and activity; in one embodiment of the present invention, a chiral phosphine ligand as described above complexed with a transition metal, preferably rhodium, iridium, ruthenium, palladium or platinium is provided.

In certain compounds of the present invention, the phosphine ligand is attached to an organic substrate or backbone by a chemical bridging group or organic substituent. For these compounds, it is preferred that the chemical bridging group or organic substituent has a linker to a polymer. The polymer-supported catalyst is a heterogenous or homogenous catalyst, dependent upon the solubility of the polymer in the reaction medium.

It is another objective of the present invention to provide a method for transition metal complex catalyzed asymmetric hydrogenation of ketones, imines, or olefin; in one embodiment, a method is provided in which such a reaction is catalyzed by a chiral phosphine ligand as described above complexed with a transition metal, preferably rhodium, iridium, ruthenium, palladium or platinium is provided.

It is yet another objective of the present invention to provide an improved method for a transition metal catalyzed asymmetric reaction such as hydrogenation, hydride transfer reaction, hydrosilylation, hydroboration, hydrovinylation, hydroformylation, hydrocarboxylation, allylic alkylation, cyclopropanation, Diels-Alder reaction, Aldol

reaction, Heck reaction, Michael addition, and stereo-selective polymerization in one embodiment, the improvement comprising catalysing the reaction with a catalyst that is a chiral phosphine ligand as described above complexed with a transition metal, preferably rhodium, iridium, ruthenium, palladium or platinium. In yet another embodiment, the catalyst is selected from the group consisting of compound 1 as illustrated in Figure 1, compound 36 as illustrated in Figure 5, compound 40 as illustrated in Figure 6, and compound 26 as illustrated in Figure 4. In another embodiment, the catalyst is a complex of a chiral phosphine complexed with a compound that is $[Rh(COD)Cl]_2$, $[Rh(COD)_2]X$ (X = BF_4, ClO_4, SbF_6, CF_3SO_3), $[Ir(COD)Cl]_2$, $[Ir(COD)_2]X$ (X = BF_4, ClO_4, SbF_6, CF_3SO_3,), $Ru(COD)Cl_2$, $[Pd(CH_3CN)_4[BF_4]_2$, $Pd_2(dba)_3$ and $[Pd(C_3H_5)Cl]_2$. And, in yet another embodiment, the catalyst is $Ru(RCOO)_2(Y)$, $RuX_2(Y)$, $Ru(methylallyl)_2(Y)$, $Ru(aryl\ group)X_2(Y)$, where where X is Cl, Br or I and Y is a chiral diphosphine of the present invention.

It is yet another objective of the present invention to provide an improved method for asymmetric hydration of a ketone, imine or olefin catalyzed by a complex comprising Ru, Rh and Ir and a chiral ligand; in one embodiment, the improvement includes conducting the catalysis with a palladium complex having a chiral phosphine ligand as described above. In yet another embodiment, the catalyst is selected from the group consisting of compound 1 as illustrated in Figure 1, compound 36 as illustrated in Figure 5, and compound 26 as illustrated in Figure 4.

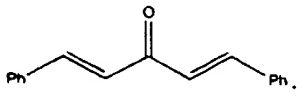
It is another method of the present invention to provide an improved method for asymmetric allyllic alkylation catalyzed by a complex comprising palladium and a chiral ligand; in one embodiment, the improvement includes catalysis with a palladium complex having a chiral ligand as described above. In yet another embodiment, the catalyst includes compound 40 as illustrated in Figure 6.

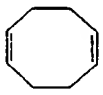
It is yet another objective of the present invention to provide an intermediate for synthesis of a chiral phosphine ligand. In one embodiment, the intermediate shown as compound 3 in Scheme 2 is provided.

Detailed Description

In the description of the cyclic chiral phosphine ligands above the term aryl includes phenyl, furan, thiophene, pyridine, pyrole, napthyl and similar aromatic rings. Substituted aryl and substituted vinyl refer to an aryl or vinyl, respectively, substituted with one or more alkyl groups having 1-8 carbon atoms, alkoxy having 1-8 carbon atoms, alkylcarbonyl having 1-8 carbon atoms, carboxy, alkoxycarbonyl having 2-8 carbon atoms, halo (Cl, Br, F or I) amino, alkylamino or dialkylamino.

An suitable aryl, divalent aryl or divalent fused aryl for use in the present invention includes but is not limited to those derived from the parent compound benzene, anthracene or fluorene. A suitable 5-membered ring heterocyclic group for use herein includes but is not limited to one derived from the parent heterocyclic compound furan, thiophene, pyrrole, tetrahydrofuran, tetrahydrothiopene, pyrrolidine, arsole or phosphole. A suitable fused heterocyclic group for use herein includes but is not limited to one derived from the parent compound bipyridine, carbazole, benzofuran, indole, benzpyrazole, benzopyran, benzopyronone or benzodiazine. A suitable aryloxy group for use in the present invention includes but is not limited to an aryl having an oxygen atom as a substituent.

"dba" is defined as  .

"COD" is defined as  .

Alkyls having 1-8 carbon atoms includes straight or branched chain alkyls and cycloalkyls having 3 to 8 carbon atoms. Representative examples are methyl, ethyl, propyl, isopropyl, butyl, tertiary butyl, pentyl, cyclopentyl, hexyl cyclohexyl and the like. The alkyl group may be substituted with phenyl, substituted phenyl or alkoxy, carboxy, alkyoxycarbonyl, halo, amino, or alkyl amino or dialkylamino as defined above.

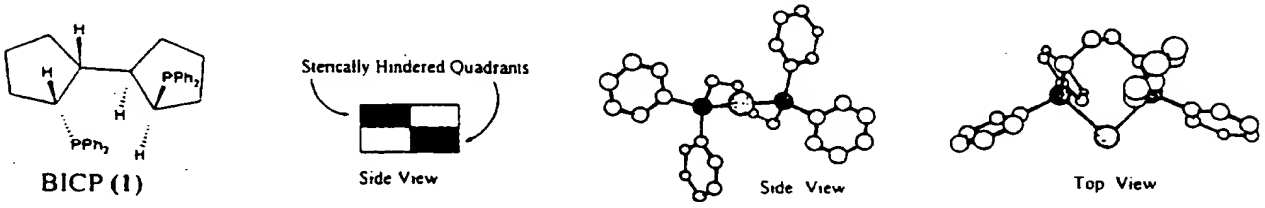
Certain compounds of the present invention provide a phosphine ligand attached to an organic substrate or backbone. In such cases, the chemical bridging group or the allyl or akyl groups adjacent to phosphine may include a linker to a polymer; the polymer supported-catalyst is a heterogenous or homogenous catalyst dependent upon the solubility of the polymer in the reaction medium.

Those skilled in the chemical art will recognize a wide variety of equivalent substituents.

The cyclic chiral phosphine ligands of the present invention are reacted with transistion metals to form catalyst. Preferably Group VIII transition metals are used and most preferably the catalyst is formed with rhodium, iridium, ruthenium, or palladium.

The invention encompasses a variety of asymmetric reactions utilizing catalyst of the invention, such as hydrogenation, hydride transfer, hydrosilylation, Grignard Cross-coupling, hydrocyanation, isomerisation, cycloadditions, Sigmatropic rearrangement, hydroboration, hydroformylation, hydrocarboxylation, allylic alkylation, hydrovinylation, cyclopropanation, aldol reaction, Heck reaction, Michael addition, and stereo-selective polymerization can be carried out with these ligand systems. The catalyst of this invention provides efficient and practical methods for producing chiral drugs for antihypertensive, antihistamine, cardiovascular and central nervous system therapies. The transition metal complexes of cyclic chiral phosphine ligands of the present invention are also important in the production of chiral agrochemicals.

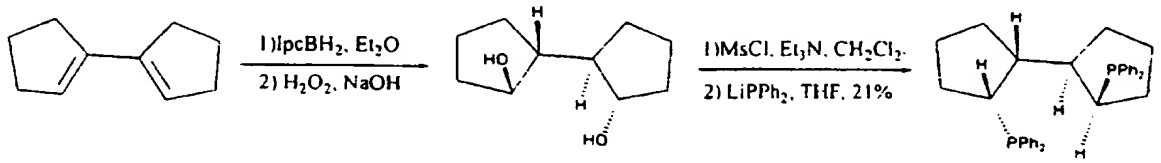
The invention is illustrated by the synthesis and application of a chiral 1,4-bisphosphine, (2R, 2'R)-bis(diphenylphosphino)-(1R, 1'R)-dicyclopentane (**1**) (abbreviated (R, R)-BICP) (Scheme 2) in the rhodium catalyzed asymmetric hydrogenation of α-(acylamino)acrylic acids. An important feature of this ligand is that it contains two cyclopentane rings in its backbone which are present to restrict its conformational flexibility leading to high enantioselectivity in asymmetric reactions.



Scheme 1

The bisphosphine ligand (**1**, R, R-BICP) was synthesized from readily available 1,1'-dicyclopentene (**2**)[11] as shown in Scheme 1. Asymmetric hydroboration of **2** using

(+)-monoisopinocamphenylborane [(+) IpcBH2] followed by oxidation with H_2O_2[12] gave the desired chiral diol (3) (100% ee after recrystallization from ether/hexanes), which was then converted to the dimesylate in high yield. Subsequent reaction of the dimesylate with lithium diphenylphospine afforded the bisphosphine 1.



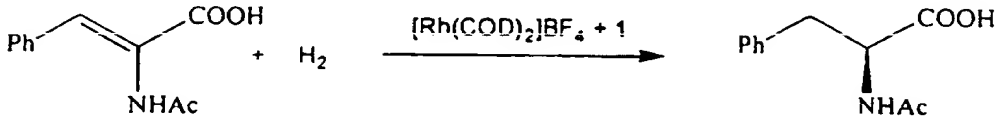
2 3 R, R- BICP 1

Scheme 2

Hydrogenation of α-acetoamidocinnamic acid was carried out at rt and 1 atm of hydrogen in the presence of the catalyst formed *in situ* from $[Rh(COD)_2]BF_4$ and bisphosphine 1 (1:1.1). Table 1 shows the results of hydrogenation of α-acetoamidocinnamic acid under a variety of conditions. The addition of a catalytic amount of triethylamine (Rh:1:Et3N=1:1.1:50) gave a better optical yield than without triethylamine (Entry 1 vs 2). This effect may be due to a conformational change in the chiral Rh complex, since the carboxylate anion generated from the substrate and triethylamine has a greater affinity for the metal than the corresponding acid.[9a] The enantioselectivity in the hydrogenation was found to be highly dependent on the nature of the Rh complex. When a neutral Rh complex was used as the catalyst precursor, the optical yield decreased dramatically (entry 3). The highest selectivity (96.8%, *S*) for the hydrogenation of α-acetoamidocinnamic acid was obtained in THF at 1 atm of H_2 in the presence of triethylamine (entry 4), while changing substrate/catalyst ratio had a small effect on the enantioselectivities (entry 4 vs 5).

TABLE 1

Optimization of the asymmetric hydrogenation of α-acetamidocinnamic acid[a]



Entry	Solvent	Et_3N (%)	ee (%)[b]
1	EtOH	---	89.2
2	EtOH	50	93.3
3[c]	EtOH	50	83.6
4	$ClCH_2CH_2Cl$	50	93.4
5	THF	50	96.8
6[d]	THF	5	95.1

a. The reaction was carried out at rt under 1 atm of H_2 for 24 h [substrate (0.5 mmol, 0.125 M):$[Rh(COD)_2]BF_4$:ligand(1) = 1:0.01:0.011]. The reaction went in quantitative yield.

b. Determined by GC using aChirasil-VAL III FSOT column on the corresponding methyl ester. The S absolute configuration was determined by comparing the optical rotation with the reported value.

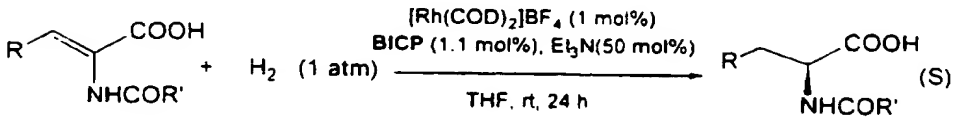
c. 0.5 mol% $[Rh(COD)Cl]_2$ was used as the catalyst precursor.

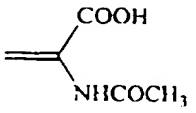
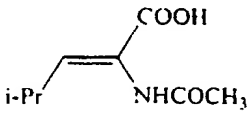
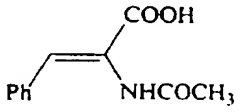
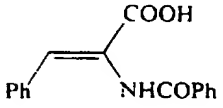
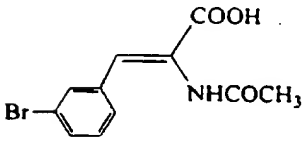
d. 0.1mol % $[Rh(COD)_2]BF_4$/0.11mol% ligand (1)/5 mol% Et_3N were used.

The methology is useful in the asymmetric synthesis of chiral amino acids. Tables 2 and 3 show the enantioselectivity of some amino acids obtained by hydrogenation of α-(acylamino)acrylic acids under an optimum condition. Enantioselectivities in this hydrogenation were not sensitive to the substitution pattern on the β-position of the prochiral olefin substrates, where α-benzamidocinnamic acid gave better optical yields than the corresponding acetoamido derivative.

TABLE 2

Asymmetric Hydrogenations of Dehydroamino Acid Derivatives

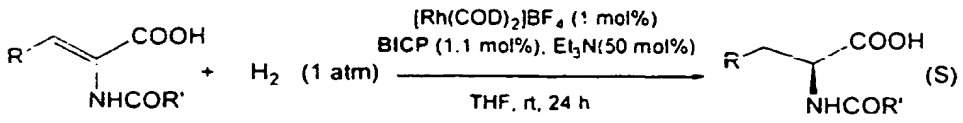


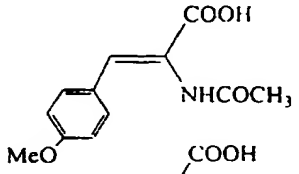
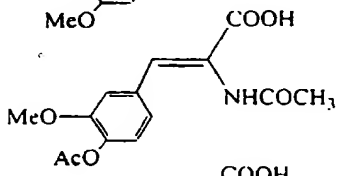
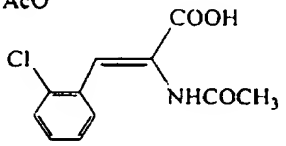
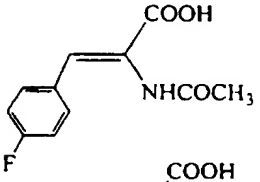
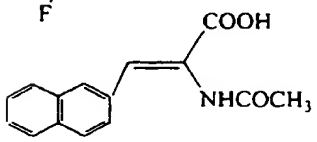
Entry	Substrate	Con. %	% ee[a]
1		100	97.5
2		100	92.6
3		100	96.8
4		100	99.0
5		100	97.0

a. % ee determined by GC using Chirasil-VAL III FSOT Column of the corresponding methyl ester.

TABLE 3

Asymmetric Hydrogenations of Dehydroamino Acid Derivatives



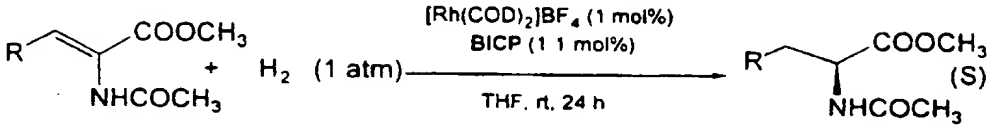
Entry	Substrate	Con. %	% ee[a]
6		100	99.0
7		100	98.2
8		100	92.5
9		100	91.6
10		100	92.9

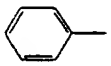
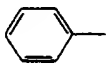
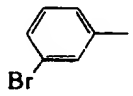
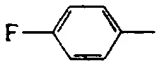
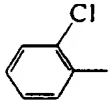
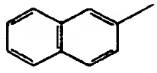
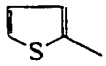
a. % ee determined by GC using Chirasil-VAL III FSOT Column of the corresponding methyl ester or by HPLC (OJ collumn)

For the corresponding methyl ester, the results are summarized in Table 4.

TABLE 4

Asymmetric Hydrogenations of Methyl Ester of Dehydroamino Acid Derivatives



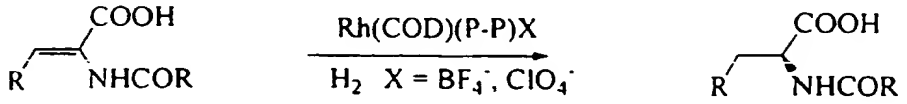
Entry	Substrate (R)	Con. %	% ee[a]
1	H	100	76.2
2		100	78.4
3[b]		100	60.0
4		100	75.1
5		100	80.5
6		100	70.9
7		100	85.3
8		100	79.1

a. % ee determined by GC using Chirasil-VAL III FSOT Column
b. 50mol% Et_3N was added

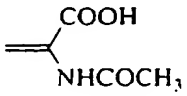
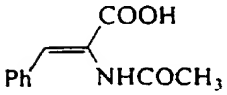
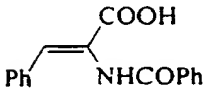
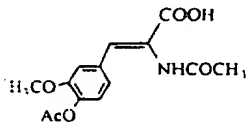
Table 5 illustrates comparative asymmetric hydrogenations of dehydroamino acid derivatives.

TABLE 5

Asymmetric Hydrogenations of Dehydroamino Acid Derivatives



P-P = chiral diphenylphosphine (% ee)

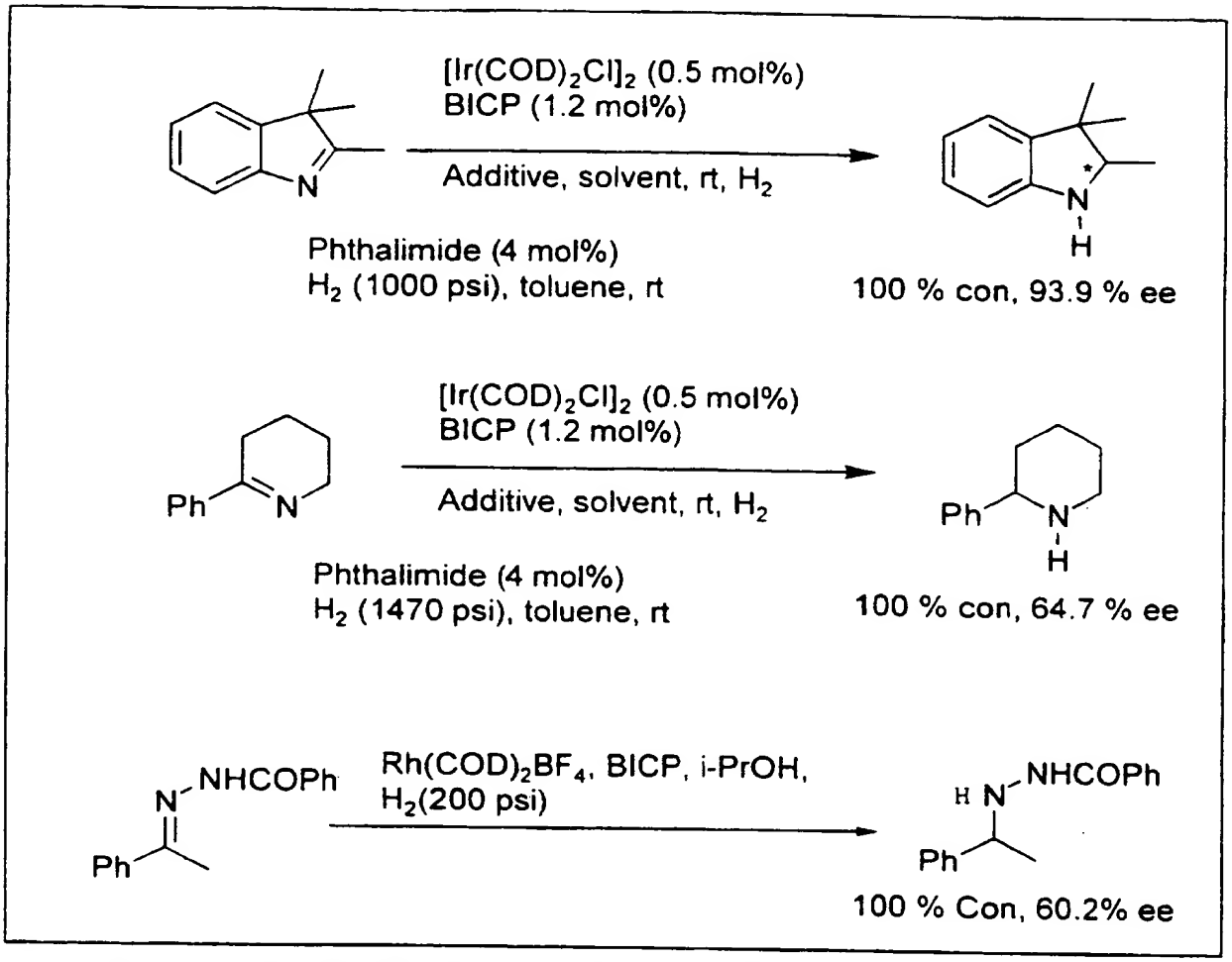
Substrate	DiPAMP	BINAP	CHIRAPHOS	BPPM	DIOP	BICP
	94	67	91	**98**	73	**98**
	95	**84**	89	91	81	**97**
	96	**100**	**99**	83	64	**99**
	94	79*	83	86	84	**98**

* NHCOPh

For the asymmetric hydrogenation of imines, rhodium iridium-complexes of BICP are effective. Table 6 provides some results on this asymmetric reaction. For an imine substrate, up to 94 % ee has achieved and this is among the highest enantioselectivity obtained with group VIII transition metal catalysts coordinated by a chiral phosphine ligand.

TABLE 6

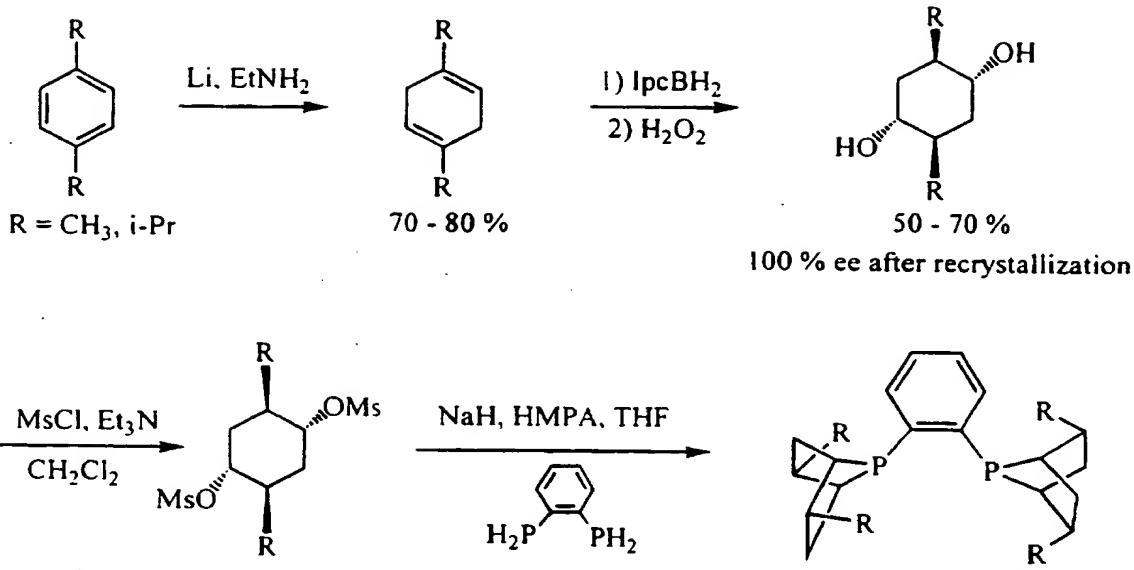
Ir and Rh-Catalyzed Asymmetric Hydrogenation of Imines



The rigid fused bicyclic [2.2.1] structure represents a new motif in chiral ligand design. Changes in the size of the R group on the ring system can modulate the asymmetric induction and high enantioselectivities can be achieved. Scheme 3 shows the synthesis of new chiral bicyclic phosphines (abbreviated as PennPhos because it represents a different structure from DuPhos [DuPont Phosphine] and was made at Penn State).

Scheme 3

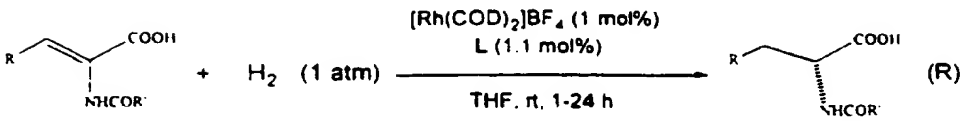
Synthesis of PennPhos

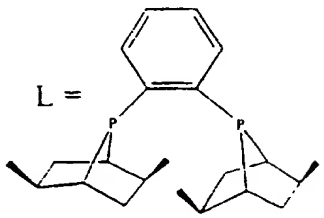


Rhodium complexes with PennPhos ligands can be used as catalyts for asymmetric hydrogenation. Table 7 lists the asymmetric hydrogenation results for dehydroamino acid derivatives.

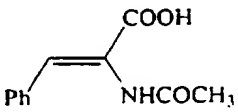
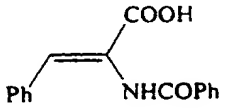
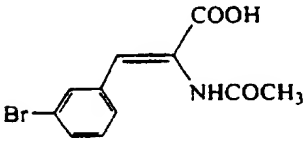
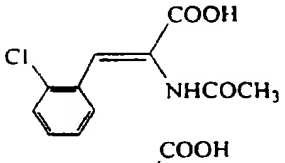
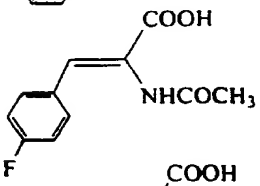
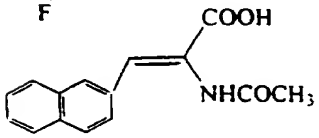
TABLE 7

Asymmetric Hydrogenations of Dehydroamino Acid Derivatives





Me-Penn Phos

Entry	Substrate	Con. %	% ee[a]
1		100	84.3
2		100	52.8
3		100	82.7
4		100	82.3
5		100	81.9
6		100	83.5

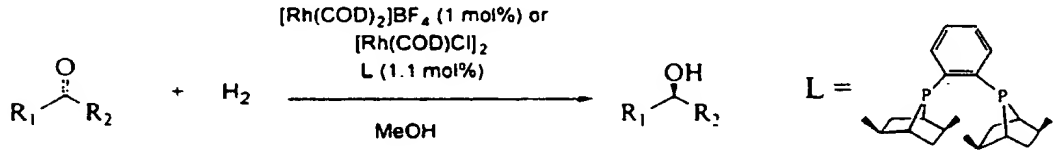
a. % ee determined by GC using Chirasil-VAL III FSOT Column of the corresponding methyl ester.

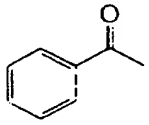
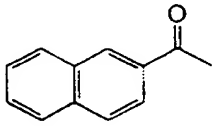
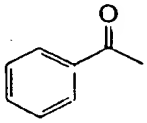
The rhodium complexes with Me-Pennphos are very effective for hydrogenation of simple ketones. Up to 97 % ee has been obtained with acetophenone, which is the

highest enantioselectivity reported in the direct asymmetric hydrogenation of simple ketones with group VIII transition metal complexes. Table 8 summarizes some results for this study.

TABLE 8

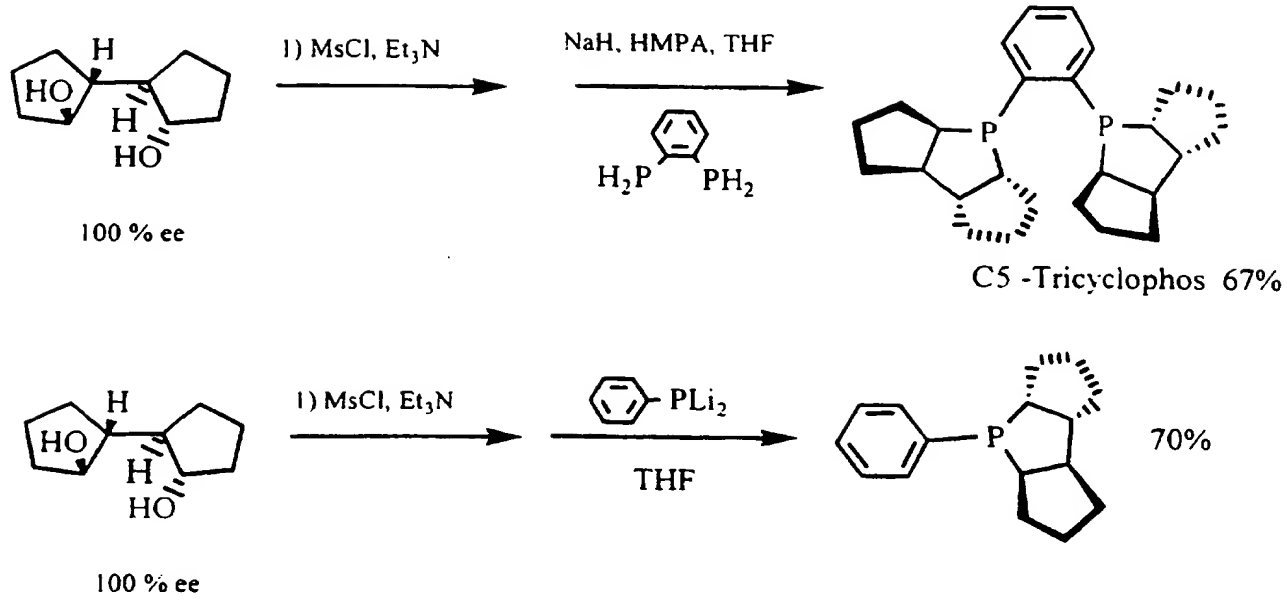
Asymmetric Hydrogenations of Simple Ketones



Entry	Substrate	Catalyst	H_2 Pressure	Con. %	% ee
1		$[Rh(COD)Cl]_2$	30 atm	97	96.5
2		$[Rh(COD)Cl]_2$	30 atm	70	91
3		$[Rh(COD)_2]BF_4$	70 atm	73	79.6

Synthesis of another chiral cyclic phosphines is illustrated in Scheme 4. The phospha-tricyclic structure is unique and the phosphines are made from chiral 1,4-diols with two rings. Tricyclic structure dictates the chiral environment around phosphines and ring size can be changed by varing the chiral diols. Both monophosphines and bisphosphines can be made from the straightforward synthetic route. They can be used as ligands for many asymmetric reactions.

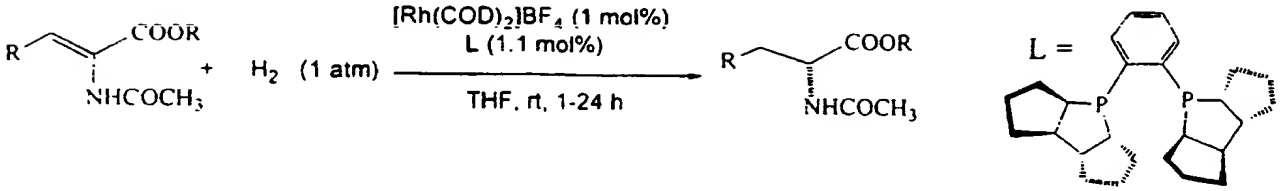
Scheme 4

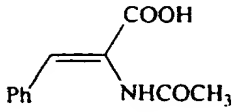
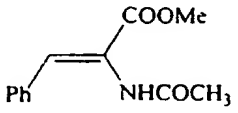


Rhodium complexes with these chiral tricyclic phosphines can be used as catalyts for asymmetric hydrogenation. Table 9 lists the asymmetric hydrogenation results for dehydroamino acid derivatives.

TABLE 9

Asymmetric Hydrogenations of Dehydroamino Acid Derivatives

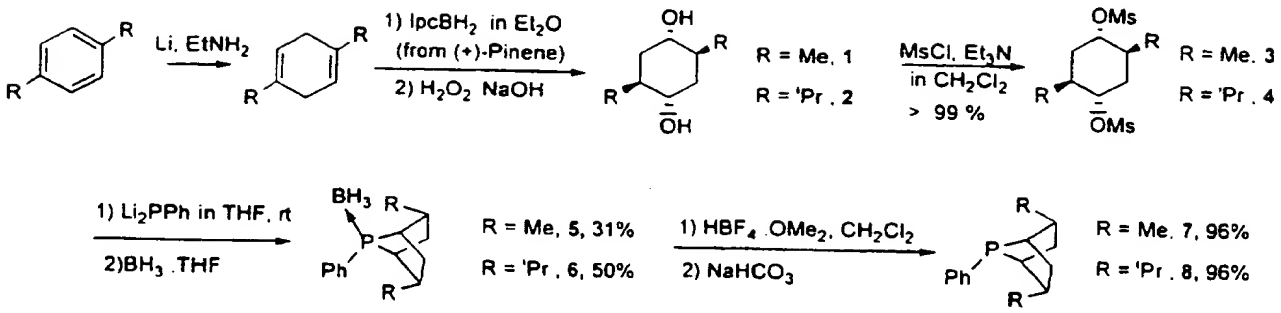


Entry	Substrate	Con. %	% ee[a]
1		100	52.9
2		100	77.6

a. % ee determined by GC using Chirasil-VAL III FSOT Column of the corresponding methyl ester.

The rigid fused bicyclic [2.2.1] structure represents a new motif in chiral ligand design. Analogous to Burk's systems, changes in the size of the R group on the ring system can modulate the asymmetric induction and high enantioselectivities can be achieved. The present invention provides the syntheses of chiral monophosphines with this fused bicyclic ring structure (Scheme 5) and their application in Pd-catalyzed asymmetric allylic alkylations.

SCHEME 5



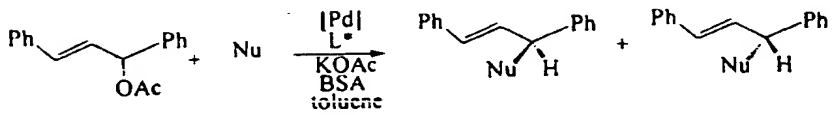
(40)

The ligand synthesis depends on the availability of enantiomerically pure cyclic 1,4-diols. Halterman[13] and Vollhardt[14] have previously prepared chiral cyclopentadiene derivatives from the chiral diols.[13-14] Halterman[13] has synthesized chiral diols **1** and **2** from the inexpensive starting materials *p*-xylene and *p*-diisopropylbenzene, respectively. The synthesis employed Birch reduction, followed by asymmetric hydroboration and recrystallization to 100 % ee. Conversion of the optically pure diols to the corresponding mesylates proceeds cleanly. Nucleophilic substitution by Li_2PPh on the chiral dimesylates **3** and **4** generated the corresponding bicyclic phosphines, which were trapped by BH_3•THF to form the air-stable boron-protected monophosphines **5** and **6**, respectively. Deprotection with a strong acid produces the desired products [**7**, (1*R*, 2*S*, 4*R*, 5*S*)-(+)-2, 5-dimethyl-7-phenyl-7-phosphabicyclo[2.2.1]heptane; **8**, (1*R*, 2*R*, 4*R*, 5*R*)-(+)-2, 5-diisopropyl-7-phenyl-7-phosphabicyclo-[2.2.1]heptane] in high yields.

Pd-catalyzed allylic alkylation was utilized to test the effectiveness of these new monophosphines as chiral ligands. Although many palladium complexes of multidentate phosphine and nitrogen ligands are excellent catalysts for this reaction,[15] palladium complexes of simple chiral monophosphines are normally not effective.[15] However, Pd-catalyzed allylic alkylation with the new monophosphine **7** gave excellent enantioselectivities and conversions (Table 10), comparable to the best results (99 % ee) reported to date.[15]

TABLE 10

Palladium-Catalyzed Asymmetric Allylic Alkylation with Chiral Monophosphines[a]



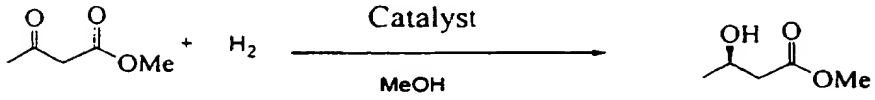
Entry	L*	[Pd]	[Pd] : L*	Nu	Additive	Time (h)	Yield (%)	% ee[b]
1	7	$Pd_2(dba)_3$	1 : 2.2	$CH_2(CO_2Me)_2$	–	1.5	96	74 (R)
2	7	$Pd(OAc)_2$	1 : 2.2	$CH_2(CO_2Me)_2$	–	4.0	98	72 (R)
3	7	$[Pd(C_3H_5)Cl]_2$	1 : 1.1	$CH_2(CO_2Me)_2$	–	5.0	97	60 (R)
4	7	$[Pd(C_3H_5)Cl]_2$	1 : 2.2	$CH_2(CO_2Me)_2$	–	2.0	93	95 (R)
5	7	$[Pd(C_3H_5)Cl]_2$	1 : 3.3	$CH_2(CO_2Me)_2$	–	1.5	96	96 (R)
6	7	$[Pd(C_3H_5)Cl]_2$	1 : 2.2	$CH_2(CO_2Me)_2$	2.8 % $AgBF_4$	1.0	80	97 (R)
7	7	$[Pd(C_3H_5)Cl]_2$	1 : 2.2	$CH_2(CO_2Me)_2$	2.8 % LiCl	2.0	95	96 (R)
8	7	$[Pd(C_3H_5)Cl]_2$	1 : 2.2	$CH_2(COMe)_2$	–	2.0	99	>97[c] (R)
9	7	$[Pd(C_3H_5)Cl]_2$	1 : 2.2	$CH(NHAc)(CO_2Et)_2$	–	2.0	95	>99.5[d] (S)
10	8	$[Pd(C_3H_5)Cl]_2$	1 : 2.2	$CH_2(CO_2Me)_2$	–	3.5	99	78 (R)

a. The reaction was carried out under N_2 using 1,3-diphenyl-2-propenyl acetate, Nu (nucleophile) (300 mol%), BSA (bis(trimethylsilyl)acetamide) (300 mol%), KOAc (2 mol%), toluene, [Pd] 1.4 mol % and L*. b. % ee was measured by HPLC using a Chiralcel OD column, and the absolute configuration was determined by comparing the optical rotation with literature values. c. % ee was measured by comparing the optical rotation with literature values. d. % ee was measured by HPLC using a Chiracel OJ column.

Ruthenium complexes with chiral phosphines are excellent catalysts for the asymmetric hydrogenation of beta keto-esters. Table 11 lists the results based on Ru-BICP catalystic system.

TABLE 11

Asymmetric Hydrogenations of beta-Keto ester



Entry	Temp	Catalyst	H_2 Pressure	Con. %	% ee
1	65 °C	Ru(BICP)Br2	1 atm	97	82
2	40 °C	Ru(BICP)Br2	5 atm	95	76
3	50 °C	Ru(BICP)Cl2	5 atm	43	84

EXAMPLES

Unless otherwise indicated, all reactions were carried out under nitrogen. THF and ether were freshly distilled from sodium benzophenone ketyl. Toluene and 1,4-dioxane were freshly distilled from sodium. Dichloromethane and hexane were freshly distilled from CaH_2. Methanol was distilled from magnesium and CaH_2. Reactions were monitored by thin-layer chromatography (TLC) analysis. Column chromatography was performed using EM silica gel 60 (230-400 mesh). ^1H NMR were recorded on Bruker ACE 200, WP 200, AM 300 and WM 360 spectrometers. Chemical shifts are reported in ppm downfield from tetramethylsilane with the solvent resonance as the internal standard ($CDCl_3$, δ 7.26 ppm). ^{13}C, ^{31}P and ^1H NMR spectra were recorded on Bruker AM 300 and WM 360 or Varian 200 or 500 spectrometers with complete proton decoupling. Chemical shifts are reported in ppm downfield from tetramethylsilane with the solvent resonance as the internal standard ($CDCl_3$, δ 77.0 ppm). Optical rotation was obtained on a Perkin-Elmer 241 polarimeter. MS spectra were recorded on a KRATOS mass spectrometer MS 9/50 for LR-EI and HR-EI. GC analysis were carried on Helwett-Packard 5890 gas chromatograph with a 30-m Supelco β-DEX™ or r-225Dex™ column. HPLC analysis were carried on Waters™ 600 chromatograph with a 25-cm CHIRALCEL OD column.

Example 1

(as depicted in Scheme 2 and Figure 8)

(1R, 1'R)-Bicyclopentyl-(2S, 2'S)-diol (3 in scheme 2)

Compound **3** was synthesized by asymmetric hydroboration of bi-1-cyclopenten-1yl using (+)-monoisopinocampheylborane ((+)-IpcBH$_2$) according to the literature procedure (Brown, H. C.; Jadhav, P. K., Mandal, A. K. *J. Org. Chem.* **1982**, *47*, 5074). The absolute configuration of the diol was assigned based on the asymmetric hydroboration of trisubstituted olefins (e.g. methylcyclopentene) using (+)-IpcBH$_2$. ^1H NMR ($CDCl_3$, 300 MHz) δ 4.04(br, 2 H), 3.84 (m, 2 H), 2.02 (m, 2 H), 1.66-1.22 (m, 10 H), 1.21 (m, 2 H); ^{13}C NMR δ 78.6, 52.2, 33.6, 29.2, 20.5; MS m/z 170 (M^+, 0.35), 152, 134, 108 , 95, 84, 68; HRMS calcd for $C_{10}H_{18}O_2$: 170.1307(M^+); found: 170.1315.

Example 2

(as depicted in Scheme 2 and Figure 8)

(1R,1'R)-Bicyclopentyl-(2S,2'S)-diol bis(methanesulfonate)

To a solution of (1R, 1'R)-bicyclopentyl-(2S, 2'S)-diol (0.8 g, 4.65 mmol) and triethylamine (1.68 mL, 12.09 mmol) in CH_2Cl_2 (30 mL) was added dropwise a solution of methanesulfonyl chloride (0.76 mL, 9.92 mmol) in CH_2Cl_2 (2 mL) at 0°C. The reaction mixture was stirred at 0°C for 30 min, and at rt for 2 h, then quenched by saturated aqueous ammonium chloride solution (25 mL). The aqueous layer was extracted with CH_2Cl_2 (3x20 mL) and the combined organic solution was dried over Na_2SO_4. After evaporation of the solvent, a white solid was obtained, which was used directly for the next step. ^1H NMR ($CDCl_3$, 200 MHz) δ 5.01(m, 2H), 3.04 (s, 6 H), 2.17 (m, 2 H), 2.15-1.65 (m, 10 H), 1.43-1.52 (m, 2 H); ^{13}C NMR δ 86.8, 48.2, 38.4, 32.8, 27.4, 22.5.

Example 3

(as depicted in Scheme 2 and Figure 8)

(1R, 1'R, 2R, 2'R)-1,1'-Bis(2-diphenylphosphino)cyclopentyl bisborane

Diphenylphosphine (1.25 mL, 7.0 mmol) in THF (80 mL) was cooled to -78°C. To this solution, n-BuLi in hexane (4.1 mL, 6.6 mmol) was added via syringe over 5 min. The resulting orange solution was warmed to rt and stirred for 30 min. After cooling the mixture to -78°C, (1R,1'R,2S,2'S)-1,1'-bicyclopentyl-2,2'-diol bismesylate (1.01 g, 3.1 mmol) in THF (20 mL) was added over 20 min. The resulting orange solution was warmed to rt and stirred overnight. The white suspension solution was hydrolyzed with saturated aqueous NH_4Cl solution. The aqueous layer was extracted with CH_2Cl_2 (2 x 20 mL). The combined organic solution was dried over anhydrous Na_2SO_4. After removal of the solvents under reduced pressure, the residue was dissolved in CH_2Cl_2 (50 mL), then treated with BH_3·THF (10 mL, 10 mmol) at rt and the mixture was stirred overnight. The reaction mixture was added to NH_4Cl aqueous solution, and extracted with CH_2Cl_2 (2 x 50 mL). The combined organic solution was dried over anhydrous Na_2SO_4. After evaporation of the solvent under reduced pressure, the residue was subjected to column chromatography on silica gel, eluting with CH_2Cl_2/hexane (1:5) and then CH_2Cl_2/hexane

(2:3) affording the product as a white solid. Yield: 0.36 g (21 %). ^{1}H-NMR ($CDCl_3$) δ 7.80-7.30 (m, 20 H, Ph), 2.55-2.35 (m, 2 H, C<u>H</u>P(BH_3)Ph_2), 1.95-1.35 (m, 14 H, CH_2 and CH), 1.7-0.5 (broad, 6 H, BH_3). ^{31}P-NMR ($CDCl_3$): δP = 17.5 (br). ^{13}C-NMR ($CDCl_3$) δ 133.43 (d, $^2J(PC)$ = 8.5 Hz, C_{ortho}), 132.25 (d, $^2J(PC)$ = 8.5 Hz, C_{ortho}), 132.08 (d, $^1J(PH)$ = 50.0 Hz, C_{ipso}), 130.67 (d, $^4J(PC)$ = 2.1 Hz, C_{para}), 130.57 (d, $^4J(PC)$ = 2.1 Hz, C_{para}), 129.71 (d, $^1J(PC)$ = 56.5 Hz, C_{ipso}), 128.39 (d, $^3J(PC)$ = 9.4 Hz, C_{meta}), 128.29 (d, $^3J(PC)$ = 9.1 Hz, C_{meta}), 46.28 (dd, J(PC) = 2.1 and 4.8 Hz, $C_{1,1'}$), 36.26 (d, $^1J(PC)$ = 30.6 Hz, $C_{2,2'}$), 31.19 (CH_2), 29.52 (CH_2), 22.51 (CH_2); MS m/z 520 (8.95), 506 (3.55), 429(19.10), 321(100), 253(7.45), 185(26.64), 108(43.68), 91(11.99), 77(6.88), HRMS cacld for $C_{28}H_{31}P_2$ (M^+-B_2H_6-Ph): 429.1901, found: 429.1906.

Example 4

(as depicted in Scheme 2 and Figure 8)

(2R, 2'R)-Bis(diphenylphosphino)-(1R, 1'R)-dicyclopentane (1)

To a solution of teh above borane complex of the phosphine (0.24 g, 0.45 mmol) in CH_2Cl_2 (4.5 mL) was added tetrafluoroboric acid-dimethyl ether complex (0.55 mL, 4.5 mmol) dropwise via syringe at -5 °C. After the addition, the reaction mixture was allowed to warm slowly to rt, and stirred for 20 h. The mixture was diluted with CH_2Cl_2, and neutralized with saturated aqueous $NaHCO_3$ solution. The aqueous layer was extracted with CH_2Cl_2. The combined organic solution was washed with brine, followed by water, and dried over Na_2SO_4. Evaporation of the solvent gave the pure phosphine. Yield: 0.21 g (93%). ^{1}H NMR ($CDCl_3$, 360 MHz) δ 7.52-7.27 (m, 20 H), 2.53 (m, 2 H), 2.27 (m, 2 H), 1.93(m, 2 H), 1.72(m, 2 H), 1.70-1.43 (m, 8 H); ^{13}C NMR ($CDCl_3$) δ 139-127 (Ph), 45.9 (d, J = 12.1 Hz), 45.8 (d, J = 12.0 Hz), 40.34 (d, J = 14.0 Hz), 30.9 (m), 23.8 (m); ^{31}P NMR ($CDCl_3$) δ -14.6. This phosphine was fully characterized by its borane complex.

Example 5

General Procedure for Asymmetric Hydrogenation

To a solution of $[Rh(COD)_2]BF_4$ (5.0 mg, 0.012 mmol) in THF (10 mL) in a glovebox was added chiral ligand **1** (0.15 mL of 0.1 M solution in toluene, 0.015 mmol), and Et_3N (0.087 mL, 0.62 mmol). After stirring the mixture for 30 min. the dehydroamino acid (1.2 mmol) was added. The hydrogenation was performed at rt under 1 atm of hydrogen for 24 h. The reaction mixture was treated with CH_2N_2, then concentrated in Vacuo. The residue was passed through a short silica gel column to remove the catalyst. The enantiomeric excesses were measured by GC using a Chirasil-VAL III FSOT column. The absolute configuration of products was determined by comparing the observed rotation with the reported value. All reactions went in quantitative yield with no by-products found by GC.

Example 6

(as depicted in Scheme 5 and Figure 12)

(1R, 2S, 4R, 5S)-(+)-2,5-Dimethyl-7-phenyl-7-phosphabicyclo[2.2.1]heptane borane (5)

To phenylphosphine (3.0 ml, 27.3 mmol) in THF (200 mL) was added n-BuLi (34.5 mL of a 1.6 M solution in hexane, 55 mmol) via syringe at -78°C over 20 min. Then the orange solution was warmed up to rt and stirred for 1 hr at rt. To the resulting orange-yellow suspension was added a solution of (1*S*,2*S*,4*S*,5*S*)-2,5-dimethyl-cyclohexane-1,4-diol bis(methanesulfonate) (**3**, 8.25 g, 27.5 mmol) in THF (100 mL) over 15 min. After the mixture was stirred overnight at rt, the pale-yellow suspension was hydrolyzed with saturated NH_4Cl solution. The mixture was extracted with ether (2 x 50 mL), and the combined organic solution was dried over anhydrous sodium sulfate. After filtration , the solvents were removed under reduced pressure. The residue was dissolved in methylene chloride (100 mL), treated with BH_3·THF (40 mL of a 1.0 M solution in THF, 40 mmol) and the mixture was stirred overnight. It was then pured into saturated NH_4Cl solution and extracted with CH_2Cl_2 (3 x 50 mL). The combined organic solution was dried over anhydrous Na_2SO_4 and filtered, the solvent was removed on reduced pressure. The residue was subjected to chromatography on silicon gel column, eluted with hexanes/CH_2Cl_2 (4:1) affording the product as a white solid. Yield: 1.95 g (31%). $[\alpha]^{25}_D$

= + 59.5° (c 1.07, $CHCl_3$). ^{1}H-NMR ($CDCl_3$) δ 7.60-7.30 (m, 5 H, $C_6\underline{H}_5$), 2.60-2.40 (m, 2 H, $C\underline{H}P(BH_3)Ph$), 2.15-2.05 (m, 1 H, $C\underline{H}$), 2.04-1.80 (m, 4 H, $C\underline{H}_2$), 1.65-1.50 (m, 1 H, $C\underline{H}$), 1.32 (d, $^3J(HH)$ = 6.5 Hz, 3 H, $C\underline{H}_3$), 0. 59 (d, $^3J(HH)$ = 6.7 Hz, 3 H, $C\underline{H}_3$), 1.6-0.2 (br, $B\underline{H}_3$); ^{13}C-NMR ($CDCl_3$) δ 131.74 (d, $^2J(PC)$ = 7.3 Hz, C_{ortho}), 130.56 (d, $^1J(PC)$ = 43.9 Hz, C_{ipso}), 129.92 (d, $^4J(PC)$ = 2.0 Hz, C_{para}), 128.44 (d, $^3J(PC)$ = 8.6 Hz, C_{meta}), 43.07 (d, $^1J(PC)$ = 30.5 Hz, $\underline{C}HP(BH_3)Ph$), 40.85 (d, $^1J(PC)$ = 31.6 Hz, $\underline{C}HP(BH_3)Ph$), 36.27 ($\underline{C}H_2$), 36.67 (d, $^3J(PC)$ = 13.5 Hz, CH_2), 35.91 (d, $^2J(PC)$ = 3.5 Hz, $\underline{C}H$), 34.65 (d, $^2J(PC)$ = 9.8 Hz, $\underline{C}H$), 20.78 ($\underline{C}H_3$) 20.53 ($\underline{C}H_3$); ^{31}P-NMR ($CDCl_3$) δ 36.3 (d, broad, $^1J(PB)$ = 58.8 Hz); HRMS Calcd for $C_{14}H_{22}BP$: 232.1552 (M^+); found: 232.1578; $C_{14}H_{19}P$: 218.1224 (M^+-BH_3); found: 218.1233.

Example 7

(as depicted in Scheme 5 and Figure 12)

(1R, 2R, 4R, 5R)-(+)-2,5-Diisopropyl-7-phenyl-7-phosphabicyclo[2.2.1]heptane borane (6)

Using the same procedure as in the preparation of **5**. Yield: 0.33 g (50%). $[\alpha]^{25}_D$ = + 25.5° (c 1.02, $CHCl_3$). ^{1}H-NMR ($CDCl_3$) δ 7.55-7.30 (m, 5 H, $C_6\underline{H}_5$), 2.85-2.70 9 (m, 2 H $C\underline{H}P(BH_3)Ph$), 2.30-2.20 (m, 1 H, $C\underline{H}$), 2.18-2.00 (m, 1 H, $C\underline{H}$), 1.95-1.65 (m, 4 H, $C\underline{H}_2$), 1.40-1.20 (m, 2 H, $C\underline{H}$), 1.03 (d, $^3J(PH)$ = 6.5 Hz, $C\underline{H}_3$), 0.87 (d, $^3J(PH)$ = 6.7 Hz, $C\underline{H}_3$), 0.85 (d, $^3J(PH)$ = 7.4 Hz, $C\underline{H}_3$), 0.53 (s, broad, 3 H, $C\underline{H}_3$), 1.5-0.2 (broad, $B\underline{H}_3$); ^{13}C-NMR ($CDCl_3$) δ 131.19 (d, $^2J(PC)$= 8.3 Hz, C_{ortho}), 130.71 (d, $^1J(PC)$ = 45.2 Hz, C_{ipso}), 129.97 (d, $^4J(PC)$ = 2.5 Hz, C_{para}), 128.45 (d, $^3J(PC)$ = 9.5 Hz, C_{meta}), 50.30 (d, $^2J(PC)$ = 2.1 Hz, CH), 48.77 (d, $^2J(PC)$ = 9.7 Hz, CH), 38.27 (d, $^1J(PC)$ = 30.5 Hz, $\underline{C}HP(BH_3)Ph$), 36.81 (CH_2), 36.71 (d, $^1J(PC)$ = 31.5 Hz, $\underline{C}HP(BH_3)Ph$), 34.73 (d, $^3J(PC)$ = 13.7 Hz, CH_2), 31.92 ($\underline{C}HMe_2$), 31.12 ($\underline{C}HMe_2$), 22.41 (CH_3), 21.55 (CH_3), 20.73 (CH_3), 20.10 (CH_3); ^{31}P-NMR ($CDCl_3$) δ 36.d (d, broad, $^1J(PB)$ = 51.4 Hz).

Example 8

(as depicted in Scheme 5 and Figure 12)

(1R, 2S, 4R, 5S)-(+)-2,5-Dimethyl-7-phenyl-7-phosphabicyclo[2.2.1]heptane (40)

To a solution of corresponding borane complex of the phosphine (5, 1.0 g, 4.31 mmol) in CH_2Cl_2 (22 mL) was added tetrafluoroboric acid-dimethyl ether complex (2.63 mL, 21.6 mmol) dropwise via a syringe at -5 °C. After the addition, the reaction mixture was allowed to warm up slowly, and stirred at rt. After 20 h, ^{31}P NMR showed the reaction was over, it was diluted by CH_2Cl_2, neutralized by saturated $NaHCO_3$ aqueous solution. The aqueous layer was extracted with CH_2Cl_2. The combined organic solution was washed with brine, followed by water, and then dried over Na_2SO_4. Evaporation of the solvent gave a pure phosphine product, which was confirmed by NMR. Yield: 0.9 g (96%). $[\alpha]^{25}_D$ = +92.5° (c 2.3, toluene); ^1H NMR ($CDCl_3$, 360 MHz) δ 7.38-7.34 (m, 2H), 7.26-7.21 (m, 2H), 7.19-7.16 (m, 1H), 2.60-2.54 (m, 2H), 1.89-1.62 (m, 5H), 1.44-1.42 (m, 1H), 1.16 (d, J = 6.12 Hz, 3H), 0.55 (d, J = 6.95 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 138.68 (d, J = 29.3 Hz), 131.42 (d, J = 13.0 Hz), 127.88 (d, J = 2.35 Hz), 126.57 (s), 47.34 (d, J = 13.5 Hz), 45.26 (d, J = 10.2 Hz), 39.21 (d, J = 6.7 Hz), 39.21 (d, J = 5.3 Hz), 38.74 (d, J = 6.7 Hz), 34.69 (d, 17.2 Hz), 22.37 (d, J = 7.8 Hz), 21.52 (s); ^{31}P NMR($CDCl_3$) δ -7.29.

Example 9

(as depicted in Scheme 5 and Figure 12)

(1R, 2R, 4R, 5R)-(+)-2,5-Diisopropyl-7-phenyl-7-phosphabicyclo[2.2.1]heptane

(8 in scheme 5)

Using the same procedure as in the preparation of 7. Yield: 1.0 g (95.5%). $[\alpha]^{25}_D$ = +43.9° (c 1.2, toluene); ^1H NMR ($CDCl_3$, 360 MHz) δ 7.35-7.30 (m, 2H), 7.24-7.14 (m, 3H), 2.94-2.85 (m, 2H), 1.76-1.53 (m, 5H), 1.25-1.14 (m, 2H), 1.06 (d, J = 7.77 Hz, 3H), 0.95-08.0 (m, 1H), 0.87 (dd, J = 3.77 Hz, 7.89 Hz, 6 H), 0.49 (d, J = 9.30 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 138.83 (d, J = 30.49 Hz), 130.69 (d, J = 12.2 Hz), 127.71 (d, J = 2.87 Hz), 126.45 (s), 53.38 (d, J = 6.34 Hz), 48.63 (d, J = 17.06 Hz), 41.97 (d, J = 13.43

Hz), 40.51 (d, J = 9.96 Hz), 37.60 (d, J = 11.09 Hz), 37.39 (d, J = 9.74 Hz), 33.03 (d, 6.11 Hz), 31.86 (s), 21.89 (s), 21.78 (s), 21.23 (s), 20.40 (s); ^{31}P NMR($CDCl_3$) δ -7.49.

Example 10

Enantioselective Allylic Alkylation

The procedures are exemplified by the experiments carried out with ligand 7 in toluene. To a stirring solution of $[Pd_2(\eta^3\text{-}C_3H_5)_2Cl_2]$ (3.0 mg, 0.008 mmol) in toluene (1.5 mL) was added ligand 7 (0.36 mL of 0.1 M solution in toluene, 0.036 mmol) under a nitrogen atmosphere. After 30 mins, racemic 1,3-diphenyl-1-acetoxypropene (150 mg, 0.60 mmol) was added. Then the solution was allowed to be stirred 30 mins. N,O-bis(trimethylsiyl)acetamide (0.44 mL, 1.8 mmol), dimethyl malonate (0.21 mL, 1.8 mmol) and potassium acetate (3 mg, 0.03 mmol) were added in this order. The reaction was monitored by TLC (eluent: Hexane / ethyl acetate = 10/1). After 1.5 hrs, TLC showed the reaction was over. After the solvent was evaporated in vacuo, column chromatography on silica gel (eluent: Hexane / ethyl acetate = 10/1) of the residue yielded the pure product : Yield: 190 mg, 97.7% . The optical purity was determined to be 95.5% ee by HPLC (Daicel Chiralcel OD column, 1 ml/min, hexane /2-propanol = 99/1).

Example 11

Typical Procedure for Hydrogenation of Imines

To a solution of chloro(1.5cyclooctadiene)iridium(I) dimer (2 mg, 0.003 mmol) in toluene (4 mL) was added a solution of BICP in toluene (0.1 M, 71 ul, 0.0071mmol), the resulting solution was stirred in glovebox for 30 min. Then phthalimide (3.5 mg, mmol) was added and the reaction mixture was stirred for another 30 min before 2,3,3-trimethylindolenine (96 ul, 0.6 mmol) was added. The reaction tube was placed in an autoclave, pressurized with hydrogen to 1000psi after several exchange with hydrogen, and stirred at rt for 65 h. Conversion (97.8%) and enantiomeric excess (92.2%) were determined by GC (a capillary column: γ-dex-225).

Example 12

(as depicted in Scheme 3, Figure 5 and Figure 11)

Me-PennPhos: 1,2-Bis{(1R,2S,4R,5S)-2,5-dimethyl-8-phenylphospha-bicyclo[2.2.1]heptyl}benzene (36a)

To the suspension of NaH (8.0 g, 333 mmol) in THF (200 ml), cooled to 0°C, was added 1,2-diphosphinobenzene (4.0 ml, 30.4 mmol), followed by HMPA (80 ml). The resulting orange suspension was stirred at 0°C for 1 h. (1S,2S,4S,5S)-2,5-dimethylcyclohexane-1,4-diol dimesolate (18.3 g, 60.9 mmol) in THF (150 ml) was added over 20 min. The resulting orange-red suspension was stirred at RT for 3.5 days, hydrolyzed with NaCl-H_2O and then extracted with hexane (2 x 100 ml). The combined organic solution was dried over Na_2SO_4. After filtration, the solvents were removed under reduced pressure. The residue was subjected to chromatography on silica gel column, eluted with hexane. Yield: 3.0 g (27.5%). ^{1}H-NMR ($CDCl_3$): δH = 7.25-7.10 (m, 2 H, aromatic), 7.08-6.95 (m, 2 H, aromatic), 3.21 (d, broad, 2 H, ^{2}J(PH) = 14.5 Hz, PCH), 2.58 (d, broad, 2 H, ^{2}J(PH) = 13.4 Hz, PCH), 1.90-1.60 (m, 12 H), 1.55-1.35 (m, 2 H,), 1.17 (d, 6 H, ^{3}J(HH) = 6.3 Hz, CH_3), 0.60 (d, 6 H, ^{3}J(HH) = 6.3 Hz, CH_3). CH. ^{13}C-NMR (is out of first order, $CDCl_3$): δC = 143.94, 143.66, 143.48, 143.20, 131.05, 131.00, 130.93, 126.33, 46,24, 46.20, 46,17, 46.13, 45.92, 45.69, 45.61, 45.38, 40.17, 40.05, 39.89, 39.73, 39.61, 39.52, 39.33, 39.29, 39.26, 34.76, 34.61. 34.51, 34.41, 34.26, 22.69, 22.65, 22.61, 20.82. ^{31}P-NMR ($CDCl_3$): δP = -7.3 ppm.

Example 13

(as depicted in Scheme 3 and Figure 11)

i-Pr-PennPhos: 1,2-Bis{(1R,2R,4R,5R)-2,5-bis-isopropyl-8-phenylphos-phabicyclo[2.2.1]heptyl}benzene (36b)

1,2-diphosphinobenzene (0.4 ml, 3.04 mmol) and NaH (0.9 g, 37.5 mmol) were mixed in THF (50 ml) and cooled to 0°C. HMPA (8.5 ml, 49 mmol) was added. The resulting orange suspension was stirred at 0°C for 1 h and then (1S,2S,4S,5S)-2,5-dimethyl-cyclohexane-1,4-diol dimesolate (2.17 g, 6.08 mmol) in THF (40 ml) was added over 10 min. The resulting orange-red suspension was stirred at RT for 3 days. After cooled to 0°C, it was hydrolyzed with NaCl-H_2O, and extracted with hexane (2 x 50 ml).

The combined organic solution was dried over Na_2SO_4 and filtered. The solvents were removed under reduced pressure. The residue was subjected to chromatography on silica gel column, eluted with hexane. Yield: 0.6 g (42%). ^{1}H-NMR ($CDCl_3$): δH = 7.20-7.10 (m, 2 H, aromatic), 7.05-6.90 (m, 2 H, aromatic), 3.38 (d, broad, 2 H, $^2J(PH)$ = 14.2 Hz, PCH), 2.85 (d, broad, 2 H, $^2J(PH)$ = 13.5 Hz, PCH), 1.85-1.45 (m, 12 H), 1.30-1.08 (m, 4 H), 1.03 (d, 6H, $^3J(HH)$ = 6.4 Hz, CH_3), 0.96 (d, 6H, $^3J(HH)$ = 5.6 Hz, CH_3), 0.86 (d, 6H, $^3J(HH)$ = 6.5 Hz, CH_3), 0.47 (s, 6 H, CH_3). ^{13}C-NMR (is out of first order, $CDCl_3$): δC = 143.97, 143.62, 143.56, 143.50, 143.45, 143.09, 130.96, 130.90, 130.86, 126.11, 54.10, 54.06, 54.03, 48.65, 48.56, 48.46, 42.02, 41.96, 41.24, 41.20, 41.18, 41.14, 37.94, 37.77, 37.60, 37.46, 33.29, 33.27, 33.24, 31.69, 23,45, 23.40, 23.35, 22.22. 20.97, 20.54. ^{31}P-NMR ($CDCl_3$): δP = -8.7 ppm.

Example 14

(as depicted in Scheme 4, Figure 4 and Figure 10)

C5-Tricyclophos: 1,2-Bis{(2R,6R,7R,11R)phosphatricyclo[3.3.0.0]undecanyl}-benzene (26)

1,2-diphosphinobenzene (0.20 ml, 1.52 mmol) and NaH (0.40 g, 16.7 mmol) were mixed in THF (50 ml) and cooled to 0°C. HMPA (4.3 ml, 25 mmol) was added. The resulting orange suspension was stirred at 0°C for 1 h and then treated with (1R,1'R,2S,2'S)-1,1'-bicyclopentyl-2,2'-diol bismesylate (0.993 g, 3.04 mmol) in THF (40 ml). The resulting orange-red suspension was stirred at RT for 20 h, pale orange-yellow suspension formed. After cooled to 0°C, it was hydrolyzed with NaCl-H_2O, and extracted with hexane (2 x 50 ml). The combined organic solution was dried over Na_2SO_4 and filtered. The solvents were removed under reduced pressure. The residue was subjected to chromatography on silica gel column, eluted with hexane/ether (40:1.5). Yield: 0.42 g (67%). ^{1}H-NMR ($CDCl_3$): δH = 7.50-7.30 (m, 2 H, aromatic), 7.25-7.10 (m, 2 H, aromatic), 3.15-2.95 (m, 2 H, PCH), 2.85-2.70 (m, 2 H, PCH), 2.50-2.30 (m, 4 H, CH), 2.05-1.00 (m, 24 H, CH_2). ^{13}C-NMR (is out of first order, $CDCl_3$): δC = . 144.03, 143.98, 130.16, 130.12, 130.08, 127.50, 53.64, 52.97, 44.72, 44.66, 44.60, 43.07, 32.64, 32.01, 31.86, 31.68, 30.58, 26.47, 25.41, 25.36, 25.31. ^{31}P-NMR ($CDCl_3$): δP = 9.6 ppm.

Example 15

General Procedure for Asymmetric Hydrogenation of Dehydroaminoacids for Pennphos ligands

In a glovebox, a schlenk reaction bottle was charged with a given amount of Rh catalyst precursor and Me-PennPhos in a ratio of 1.1 mol ligand per 1 mol Rh and 10 ml of the given solvent (dried and degassed), the resulting orange-yellow solution was stirred at rt for 20 min. Then substrate (1 mmol, sub/cat = 100) was added. The nitrogen atmosphere was exchanged to H_2 by flashing the schlenk with H_2. The reaction mixture was then stirred at RT and 1 atm H_2 for a certain period of time. The reaction solution was passed through a short silica gel, washed with ether. The conversion and ee were measured by GC analysis on Chirasil-Val III column. The absolute configuration was determined by measuring the rotation of product and comparing with the corresponding standard values.

Example 16

General Procedure for Asymmetric Hydrogenation of Ketones

In a glovebox, a reaction bottle was charged with $[Rh(COD)Cl]_2$ (2.5 mg, 0.0101 mmol) and Me-PennPhos (3.7 mg, 0.0103 mmol), and MeOH (10 ml, dried and degassed), the resulting orange-yellow solution was stirred at rt for 30 min. Then ketone substrate (1 mmol, substrate /catalyst = 100) was added. The reaction solution was then placed in an autoclave. The nitrogen atmosphere was exchanged to H_2 by flashing the autoclave with H_2 (10 to 20 atm). The autoclave was pressurized to a certain atmosphere of H_2. The reaction mixture was then stirred at RT for a given period of time. The reaction solution was then passed through a short silica gel, washed with ether. The conversion and ee were measured by GC analysis on chiral β–dex 120 column. The absolute configuration was determined by measuring the rotation of product and comparing with the corresponding standard values.

Example 17

General Procedure for Asymmetric Hydrogenation of beta-Keto esters

BICP (0.01 mol) and Ru(COD)(2-methylallyl)$_2$ (0.01 mol) were placed in a 10 ml Schlenk tube and the vessel was purged with argon. 2 mL of anhydrous acetone were added. To this suspension was added methanolic HBr (0.11 ml of a 0.29 M solution) and the suspension was stirred 30 min at rt. The solvent was thoroughly evaporated under vacuum and the Ru(BICP)Br$_2$ obtained was used immediately. The solution of appropriate substrate (1 mmol) in degassed solvent (2 ml) was placed in a 10 ml Schlenck tube and degasses by 3 cycles of vacuum/ argon. This mixture was added to the catalyst (1%) in a glass vessel and placed under argon in 300 ml stainless steel autoclave. The Argon atmosphere was replaced with hydrogen. The hydrogenations were run under the reaction conditions given The solvent was removed under pressure. Conversion and ee are determined by chiral GC column β-dex 120 and γ-dex 225.

The above examples illustrate the present invention and are not intended to limit the invention in spirit or scope.

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CLAIMS

What is claimed is:

1. A chiral phosphine ligand comprising a conformationally rigid cyclic structure, wherein the phosphorus is bonded to or is part of the cyclic structure, whereby the ligand rigidity provides enhanced chiral discrimination in metal catalyzed asymmetric organic reactions, and wherein the phosphine ligand is selected from the group consisting of a chiral phosphine ligand comprising:

   i) a) a 2,2'-bis(diorganophosphino)-1,1'-bis(cyclic) structure wherein each cycle of the bis(cyclic) structure comprises 3 to 8 carbon atoms wherein the 1, 1', 2 and 2' carbon atoms in the bis(cyclic) structure are saturated carbon atoms and wherein the carbon atoms in the bis(cyclic) structure other than the 1, 1', 2 and 2' carbon atoms are optionally replaced with nitrogen;

   b) a 1,1'-bis(cyclic)-2,2'(organophosphinite) structure;

   c) a chiral phosphine ligand comprising a heteroatom-containing spiro bis-organophosphine or organophosphinite;

   d) a chiral bidentate phosphine ligand comprising a (bis)phospha-tricyclic structure with a bridge group;

   e) a chiral phosphine ligand comprising a (bis)fused phospha-bicyclic structure comprising a bridge structure;

   f) a chiral phosphine ligand comprising a cis(bis) phosphine fused bicyclic structure;

   g) a chiral phosphine ligand comprising a trans(bis) phosphine bicyclic structure;

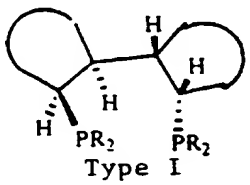
   h) a chiral phosphine ligand comprising a cis or trans biphosphine cyclic structure having two R' substituents selected from the group consisting of alkyl, fluoroalkyl or perfluoroalkyl, each having up to 8 carbon atoms, aryl, substituted aryl, arylalkyl, ring-substituted arylalkyl, and $-CR'_2(CR'_2)_qZ(CR'_2)_pR'$ wherein q and p are the same or different integers ranging from 1 to 8; Z is defined as O, S, NR, PR, AsR, SbR, divalent aryl, divalent fused aryl, divalent 5-membered ring heterocyclic

group, or a divalent fused heterocyclic group where R is selected from the group consisting of alkyl of 1-8 carbon atoms, aryl, and substituted aryl; or

ii) a chiral monodentate phosphine ligand comprising a phospha-tricyclic structure.

2. A cyclic phosphine ligand of claim 1 having a structure selected from the group consisting of :

A. Bidentate cyclic chiral phosphines:



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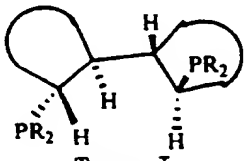

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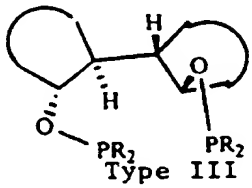

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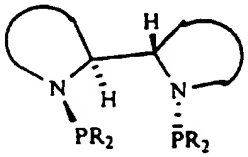

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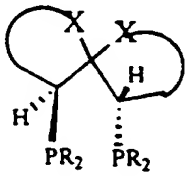

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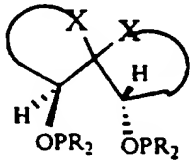

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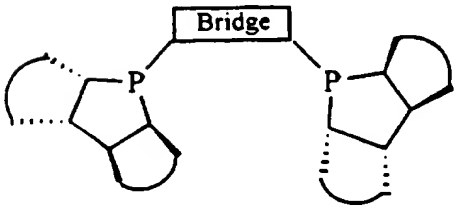

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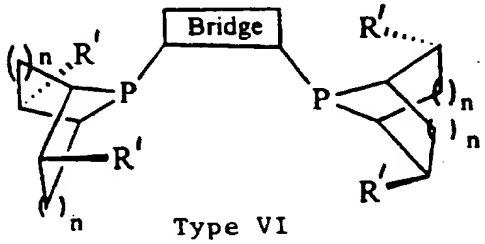

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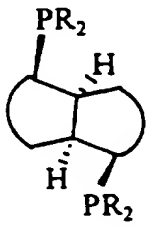

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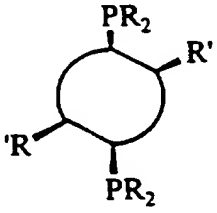

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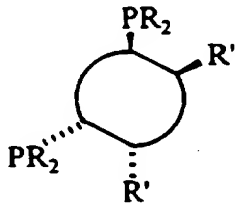
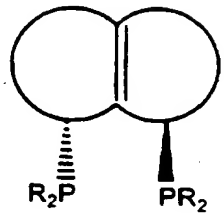


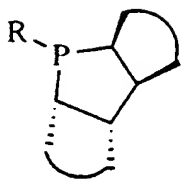
Type VIIb



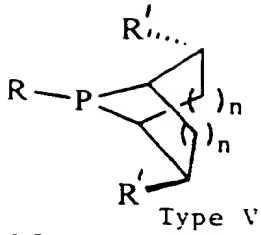
Type VIIc

or

B. monodentate cyclic chiral phosphines



Type V



Type VI

wherein each R is independently selected from the group consisting of alkyl of 1-8 carbon atoms, aryl, and substituted aryl;

each R' is independently selected from the group consisting of alkyl, fluoroalkyl and perfluoroalkyl, each having up to 8 carbon atoms; aryl; substituted aryl; arylalkyl; ring-substituted arylalkyl; and $-CR'_2(CR'_2)_qZ(CR'_2)_pR'$ wherein q and p are the same or different integers ranging from 1 to 8, R' is as defined above, and Z is selected from the group consisting of O, S, NR, PR, AsR, SbR, divalent aryl, divalent fused aryl, divalent 5-membered ring heterocyclic group, and a divalent fused heterocyclic group where R is as defined above;

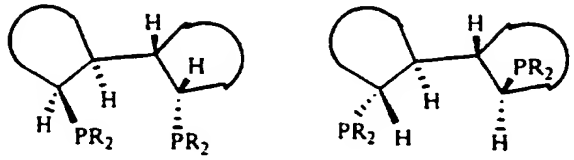
the cyclic structure D represents a ring having 3 to 8 carbon atoms and the cyclic structure ⊃ represents a ring having 0 to 8 carbon atoms; each of which may be substituted within the ring with one or more oxygen, sulfur, N-R', C=O, or CR'_2, wherein the ring may further be substituted with R' as defined above;

the Bridge is selected from the group consisting of $-(CH_2)_r-$ where r is an integer ranging from 1 to 8; $-(CH_2)_sZ(CH_2)_m-$ wherein s and m are each the same or different integers ranging from 1 to 8; 1,2-divalent phenyl; 2,2'divalent-1,1'biphenyl; 2,2'divalent 1,2'binapthyl; and ferrocene; each of which may be substituted with R' as defined above; and wherein the substitution on 1,2-divalent phenyl, the ferrocene or biaryl bridge is independently selected from the group consisting of hydrogen, halogen, alkyl, alkoxyl, aryl, aryloxy, nitro, amino, vinyl, substituted vinyl, alkynyl, or sulfonic acids;

X is selected from the group consisting of O, S and NR where R is as defined above; and,

n is 1 or 2.

3. A cyclic chiral phosphine ligand, according to claim 1, having the following structure:

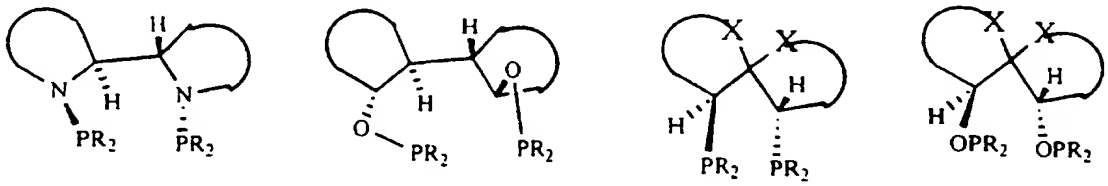


wherein each R is independently selected from the group consisting of aryl, substituted aryl, or alkyl of 1-8 carbon atoms;

the cyclic structure D represents a ring having 3 to 8 carbon atoms which may be substituted within the ring with one or more oxygen, sulfur, N-R', C=O, or CR'_2, wherein the ring may further be substituted with R' wherein R' is selected from the group consisting of alkyl, fluoroalkyl and perfluoroalkyl, each having up to 8 carbon atoms; aryl; substituted aryl; arylalkyl; ring-substituted arylalkyl; and $-CR'_2(CR'_2)_qZ(CR'_2)_pR'$ wherein q and p are the same or different integers ranging from 1 to 8, R' is as defined above, and Z is selected from the group consisting of O, S, NR, PR, AsR, SbR, divalent aryl, divalent fused aryl, divalent 5-membered ring heterocyclic group, and a divalent fused heterocyclic group where R is as defined above.

4. A cyclic chiral phosphine ligand, according to claim 3, selected from the group consisting of structures 1-13 as illustrated in Figure 2.

5. A cyclic phosphine ligand, according to claim 1, having the following structure:



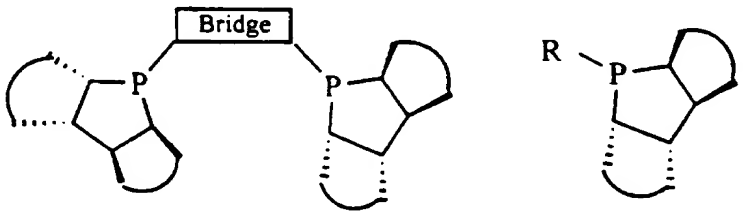
wherein each R is independently selected from the group consisting of aryl, substituted aryl, or alkyl of 1-8 carbon atoms;

the cyclic structure D represents a ring having 3 to 8 carbon atoms which may be substituted within the ring with one or more oxygen, sulfur, N-R', C=O, or CR'_2, wherein the ring may further be substituted with R' wherein R' is selected from the group consisting of alkyl, fluoroalkyl and perfluoroalkyl, each having up to 8 carbon atoms; aryl; substituted aryl; arylalkyl; ring-substituted arylalkyl; and $-CR'_2(CR'_2)_qZ(CR'_2)_pR'$ wherein q and p are the same or different integers ranging from 1 to 8, R' is as defined above, and Z is selected from the group consisting of O, S, NR, PR, AsR, SbR, divalent aryl, divalent fused aryl, divalent 5-membered ring heterocyclic group, and a divalent fused heterocyclic group where R is as defined above; and,

X is selected from the group consisting of O, S and NR where R is as defined above.

6. A cyclic chiral phosphine ligand, according to claim 5, which is selected from the group consisting of structures 14-23 as illustrated in Figure 3.

7. A cyclic phosphine ligand, according to claim 1, having the following structure:



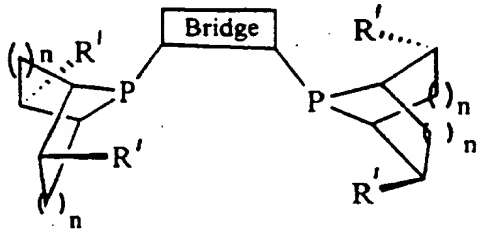
wherein each R is independently selected from the group consisting of aryl, substituted aryl, or alkyl of 1-8 carbon atoms;

the cyclic structure D represents a ring having 3 to 8 carbon atoms which may be substituted within the ring with one or more oxygen, sulfur, N-R', C=O, or CR'_2, wherein the ring may further be substituted with R' wherein R' is selected from the group consisting of alkyl, fluoroalkyl and perfluoroalkyl, each having up to 8 carbon atoms; aryl; substituted aryl; arylalkyl; ring-substituted arylalkyl; and $-CR'_2(CR'_2)_qZ(CR'_2)_pR'$ wherein q and p are the same or different integers ranging from 1 to 8, R' is as defined above, and Z is selected from the group consisting of O, S, NR, PR, AsR, SbR, divalent aryl, divalent fused aryl, divalent 5-membered ring heterocyclic group, and a divalent fused heterocyclic group where R is as defined above; and,

the Bridge is selected from the group consisting of $-(CH_2)_r-$ where r is an integer ranging from 1 to 8; $-(CH_2)_sZ(CH_2)_m-$ wherein s and m are each the same or different integers ranging from 1 to 8; 1,2-divalent phenyl; 2,2'divalent-1,1'biphenyl; 2,2'divalent 1,2'binapthyl; and ferrocene; each of which may be substituted with R' as defined above; and wherein the substitution on 1,2-divalent phenyl, the ferrocene or biaryl bridge is independently selected from the group consisting of hydrogen, halogen, alkyl, alkoxyl, aryl, aryloxy, nitro, amino, vinyl, substituted vinyl, alkynyl, or sulfonic acids.

8. A cyclic chiral phosphine ligand, according to claim 7, which is selected from the group consisting of structures 24-34 as illustrated in Figure 4.

9. A cyclic phosphine ligand, according to claim 1, having the following structure:



wherein each R' is independently selected from the group consisting of alkyl, fluoroalkyl and perfluoroalkyl, each having up to 8 carbon atoms; aryl; substituted aryl; arylalkyl; ring-substituted arylalkyl; and $-CR'_2(CR'_2)_qZ(CR'_2)_pR'$ wherein q and p are the same or

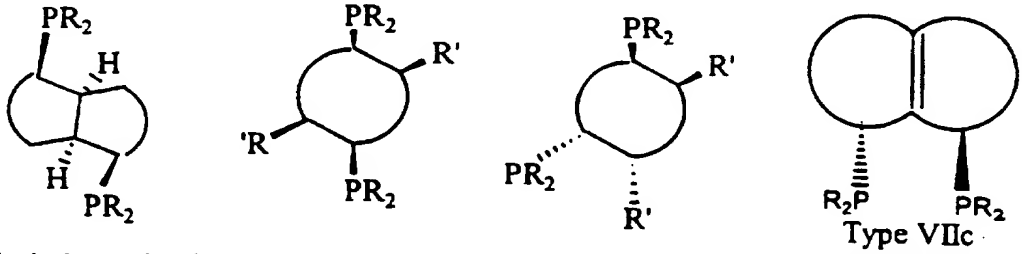
different integers ranging from 1 to 8, R' is as defined above, and Z is selected from the group consisting of O, S, NR, PR, AsR, SbR, divalent aryl, divalent fused aryl, divalent 5-membered ring heterocyclic group, and a divalent fused heterocyclic group where R is as defined above;

the Bridge is selected from the group consisting of $-(CH_2)_r-$ where r is an integer ranging from 1 to 8; $-(CH_2)_sZ(CH_2)_m-$ wherein s and m are each the same or different integers ranging from 1 to 8; 1,2-divalent phenyl; 2,2'divalent-1,1'biphenyl; 2,2'divalent 1,2'binapthyl; and ferrocene; each of which may be substituted with R' as defined above; and wherein the substitution on 1,2-divalent phenyl, the ferrocene or biaryl bridge is independently selected from the group consisting of hydrogen, halogen, alkyl, alkoxyl, aryl, aryloxy, nitro, amino, vinyl, substituted vinyl, alkynyl, or sulfonic acids; and,

n is 1 or 2.

10. A cyclic chiral phosphine ligand, according to claim 9, which is selected from the group consisting of structures 35-39 of Figure 5.

11. A cyclic phosphine ligand, according to claim 1, having the following structure:



Type VIIc

wherein each R is independently selected from the group consisting of aryl, substituted aryl, or alkyl of 1-8 carbon atoms;

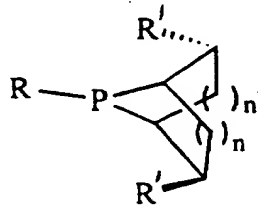
each R' is independently selected from the group consisting of alkyl, fluoroalkyl and perfluoroalkyl, each having up to 8 carbon atoms; aryl; substituted aryl; arylalkyl; ring-substituted arylalkyl; and $-CR'_2(CR'_2)_qZ(CR'_2)_pR'$ wherein q and p are the same or different integers ranging from 1 to 8, R' is as defined above, and Z is selected from the

group consisting of O, S, NR, PR, AsR, SbR, divalent aryl, divalent fused aryl, divalent 5-membered ring heterocyclic group, and a divalent fused heterocyclic group where R is as defined above; and,

the cyclic structure D represents a ring having 3 to 8 carbon atoms and the cyclic structure D represents a ring having 0 to 8 carbon atoms; each of which may be substituted within the ring with one or more oxygen, sulfur, N-R', C=O, or CR'_2, wherein the ring may further be substituted with R' as defined above.

12. A cyclic chiral phosphine ligand, according to claim 11, which is selected from the group consisting of structures 45-49 of Figure 7.

13. A cyclic phosphine ligand, according to claim 1, having the following structure:



wherein R is independently selected from the group consisting of aryl, substituted aryl, or alkyl of 1-8 carbon atoms;

each R' is independently selected from the group consisting of alkyl, fluoroalkyl and perfluoroalkyl, each having up to 8 carbon atoms; aryl; substituted aryl; arylalkyl; ring-substituted arylalkyl; and $-CR'_2(CR'_2)_qZ(CR'_2)_pR'$ wherein q and p are the same or different integers ranging from 1 to 8, R' is as defined above, and Z is selected from the group consisting of O, S, NR, PR, AsR, SbR, divalent aryl, divalent fused aryl, divalent 5-membered ring heterocyclic group, and a divalent fused heterocyclic group where R is as defined above;and,

n is 1 or 2.

14. A cyclic chiral phosphine ligand, according to claim 13, which is selected from the group consisting of structures 40-44 as illustrated Figure 6.

15. A catalyst comprising a ligand of claim 1 complexed with a transition metal.

16. The catalyst of claim 15 wherein the transition metal is selected from the group consisting of rhodium, iridium, ruthenium, palladium and platinium.

17. In a method for transition metal complex catalyzed asymmetric hydrogenation of ketones, imines, or olefin, the improvement comprising catalysing the reaction with the catalyst of claim 16.

18. In a method for a transition metal catalyzed asymmetric reaction selected from the group consisting of hydrogenation, hydride transfer reaction, hydrosilylation, hydroboration, hydrovinylation, hydroformylation, hydrocarboxylation, allylic alkylation, cyclopropanation, Diels-Alder reaction, Aldol reaction, Heck reaction, Michael addition, and stereo-selective polymerization, the improvement comprising catalysing the reaction with a catalyst of claim 16.

19. A method of claim 18 wherein said catalyst is selected from the group consisting of compound 1 as illustrated in Figure 1, compound 36 as illustrated in Figure 5, compound 40 as illustrated in Figure 6, and compound 26 as illustrated in Figure 4.

20. A method of claim 18 wherein the catalyst is a complex of a chiral phosphine complexed with a compound selected from the group consisting of $[Rh(COD)Cl]_2$, $[Rh(COD)_2]X$; $[Ir(COD)Cl]_2$; $[Ir(COD)_2]X$, $Ru(COD)Cl_2$, $[Pd(CH_3CN)_4[BF_4]_2$, $Pd_2(dba)_3$, and $[Pd(C_3H_5)Cl]_2$; wherein X is selected from the group consisting of BF_4, ClO_4, SbF_6, and CF_3SO_3.

21. A method of claim 18 wherein the catalyst is a compound selected from the group consisting of $Ru(RCOO)_2(Y)$, $RuX_2(Y)$, $Ru(methylallyl)_2(Y)$, $Ru(aryl\ group)X_2(Y)$, wherein X is selected from the group consisting of Cl , Br and I; and, Y is a chiral diphosphine of claim 1.

22. In a method for asymmetric hydration of a ketone, imine or olefin catalyzed by a complex comprising Ru, Rh and Ir and a chiral ligand, the improvement comprising conducting the catalysis with a palladium complex having a chiral phosphine ligand of claim 1.

23. A method of claim 22 wherein said catalyst is selected from the group consisting of compound 1 as illustrated in Figure 1, compound 36 as illustrated in Figure 5, and compound 26 as illustrated in Figure 4.

24. In a method for asymmetric allyllic alkylation catalyzed by a complex comprising palladium and a chiral ligand, the improvement comprising conducting the catalysis with a palladium complex having the chiral ligand of claim 1.

25. A method of claim 24 wherein said catalyst is compound 40 as illustrated in Figure 6.

26. The chiral phosphine ligand shown as compound 1 in Figure 1.

27. The chiral phosphine ligand shown as compound 36 in Figure 5.

28. The chiral phosphine ligand shown as compound 40 in Figure 6.

29. The chiral phosphine ligand shown as compound 26 in Figure 4.

30. The intermediate shown as compound 3 in Scheme 2.

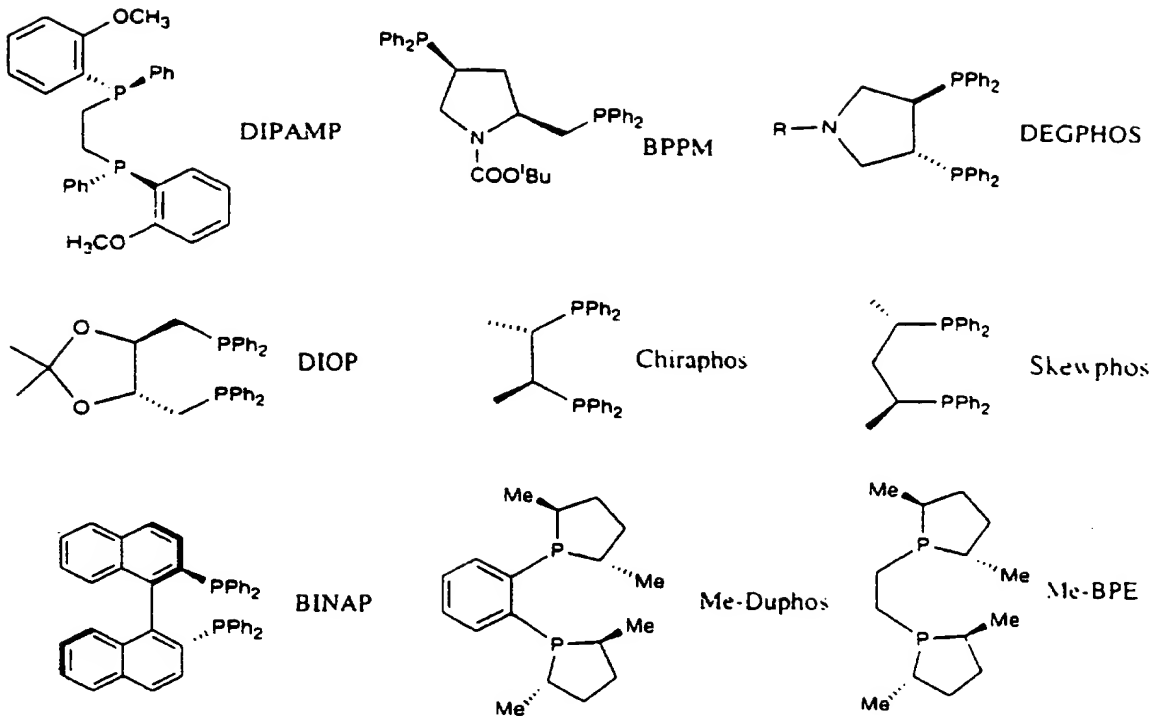
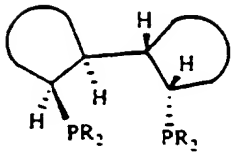
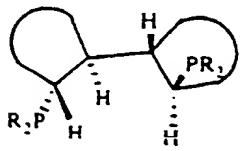


Figure 1. Chiral bidentate phosphine ligands

Type I Bidentate Cyclic Phosphines



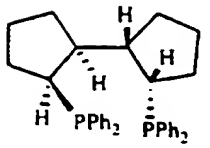
and



= ring structure (ring size from 3 to 8) containing alkyl, aryl, heteroatoms or additional chiral centers

R = Aryl, Alkyl, substituted aryl or alkyl

Examples



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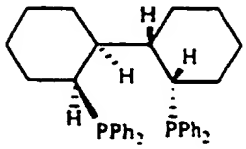

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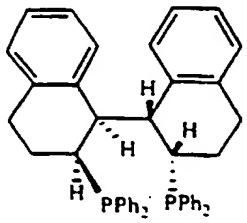

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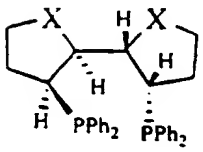

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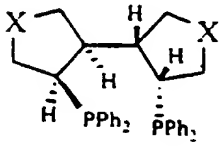

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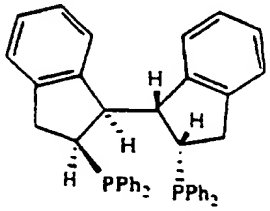

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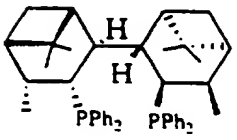

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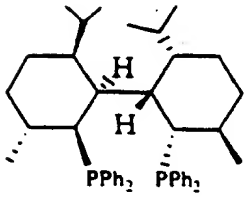

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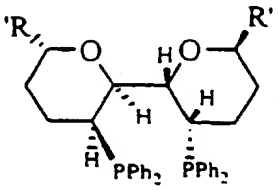

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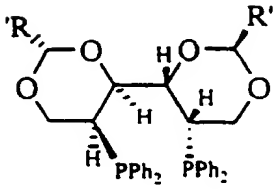

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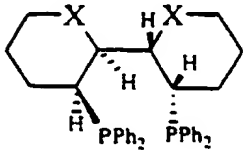

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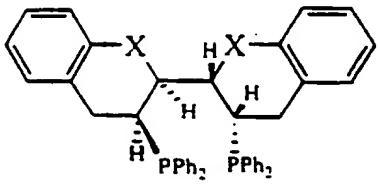

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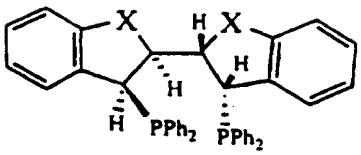
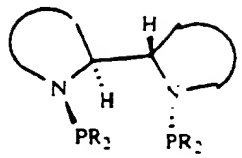


13

X = O, NR, S, CR_2, C=O, etc.

Figure 2. Selected New phosphine ligands with ring structures

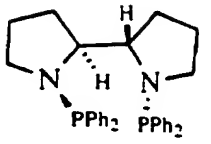
Type II



D = ring structure (ring size from 3 to 8) containing alkyl, aryl, heteroatoms or additional chiral centers

X = O, NR, S, CR_2, C=O, etc.

Examples



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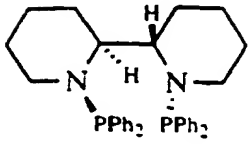

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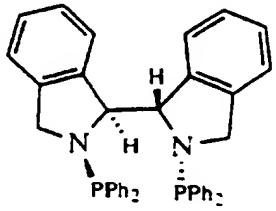

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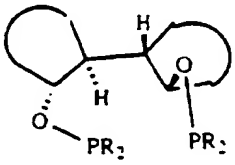
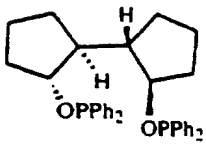
Type III





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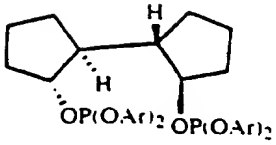

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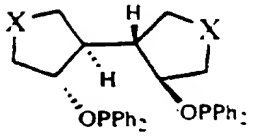
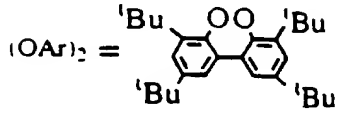
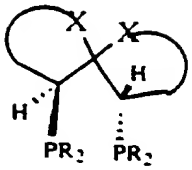
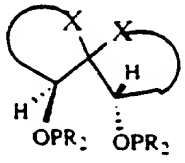


19

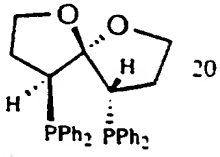


Type IV





X = O, or NR



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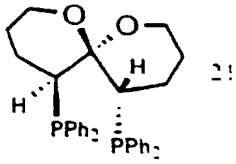
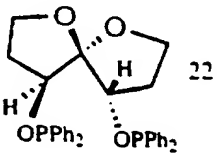


21

Spiro Phosphines



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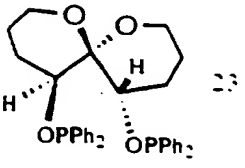
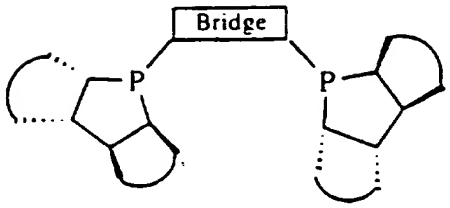


23

Figure 3. Selected new phosphine ligands with ring structures

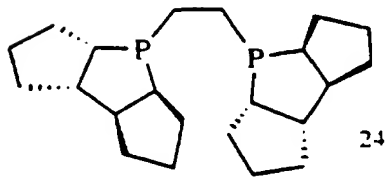
Type V Bidentate Cyclic Phosphines



) = ring structure (ring size from 0 to 8) containing alkyl, aryl, heteroatoms or additional chiral centers

Bridge = Alkyl (e.g., -(CH2)n-, n = 2, 3, 4). Aryl (e.g., benzene, ferrocene, etc.)

Examples



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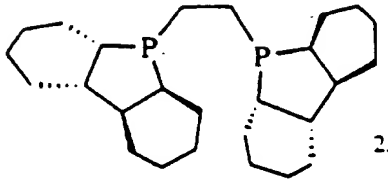

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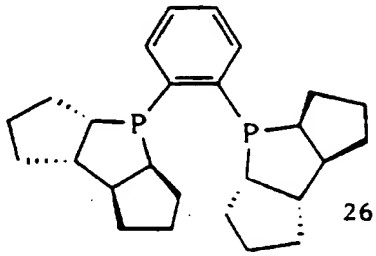

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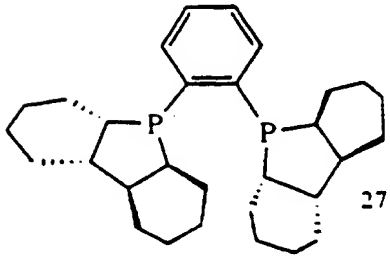

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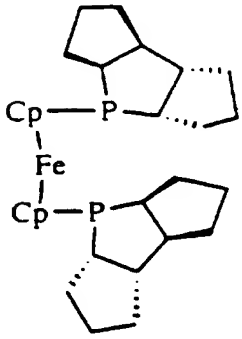

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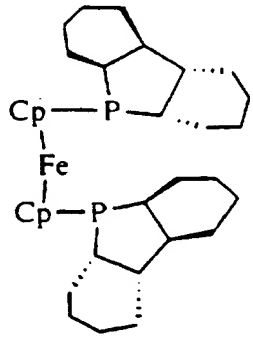

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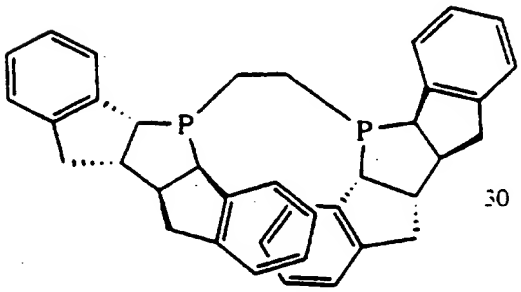

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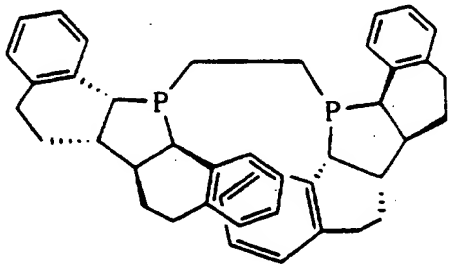
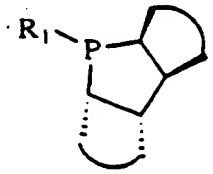


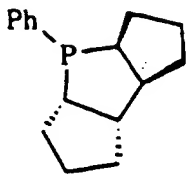
31

Type V Monodentate Chiral Phosphines

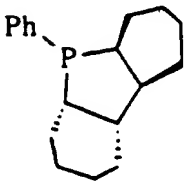


R1 = aryl or alkyl groups or substituted aryl or alkyl groups

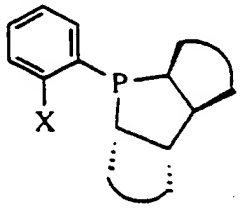
Examples



32



33

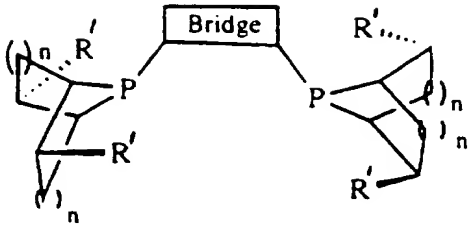


X = chiral oxazolines, COOH, OMe, OH, SMe, SH, NR'_2, PPh_2

34

Figure 4. Selected new phosphine ligands with ring structures

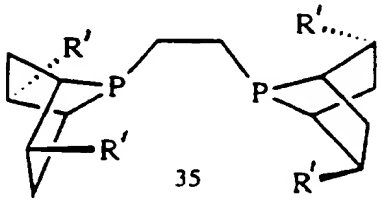
Type VI Bidentate Cyclic Phosphines

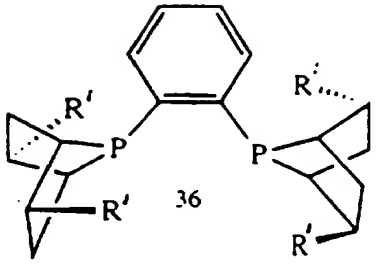


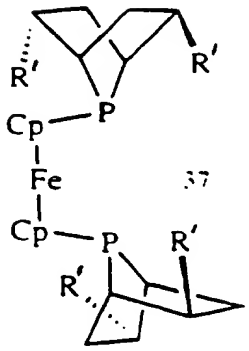
Bridge = Alkyl (e.g., -(CH2)n-, n = 2, 3, 4); Aryl (e.g., benzene, ferrocene, etc.)

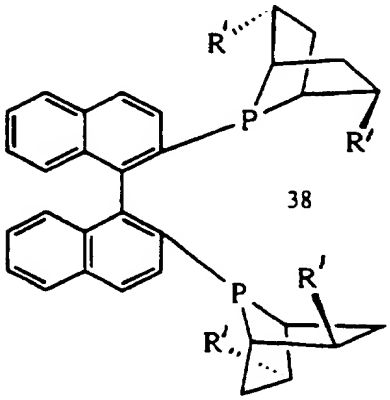
n = 1, 2

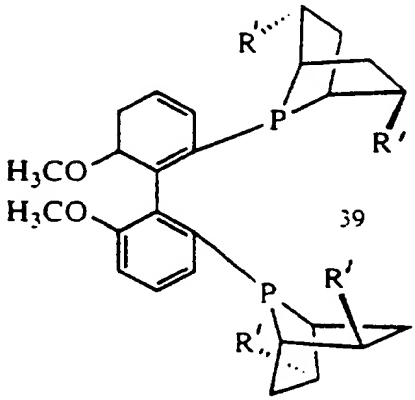
Examples







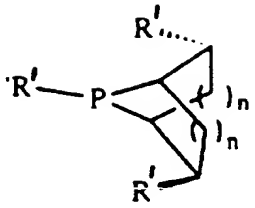




R' = CH_3, Et, i-Pr, Ph, etc.

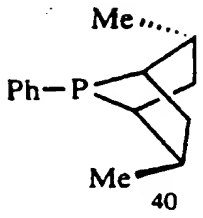
Figure 5. Selected new phosphine ligands with ring structures

Type VI Monodentate Cyclic Phosphines



n = 1, 2

Examples



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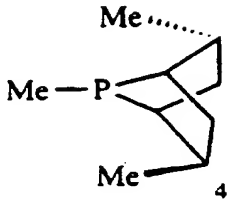

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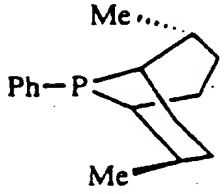

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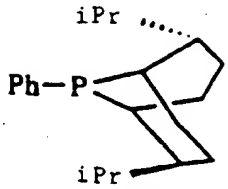
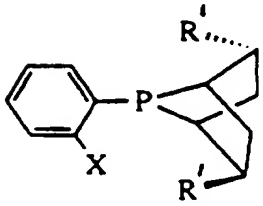


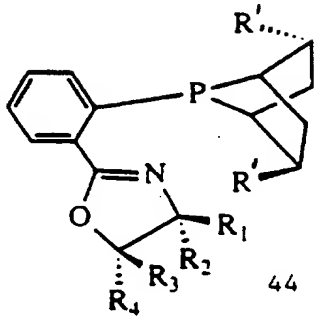
40a

R', R = aryl or alkyl groups (e.g., CH_3, Et, i-Pr, Ph, etc.) and substitituted aryl or alkyl groups



43

X = chiral oxazolines, COOH, OMe, OH, SMe, SH, NR'_2, PPh_2

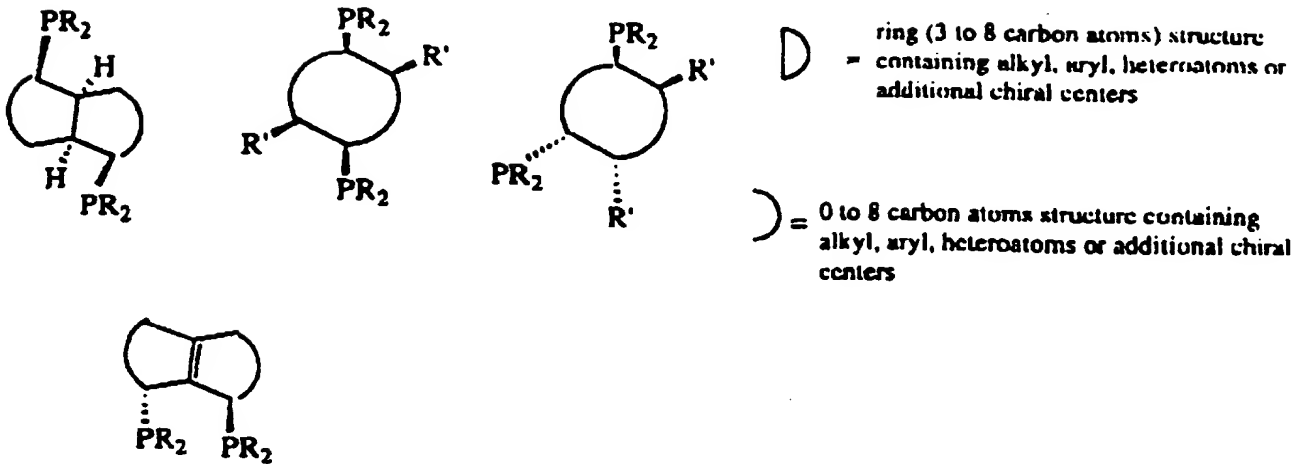


44

R_1, R_2, R_3, R_4 = aryl or alkyl groups

Figure 6. Selected new phosphine ligands with ring structures

Type VII Bidentate Cyclic Phosphines



Examples

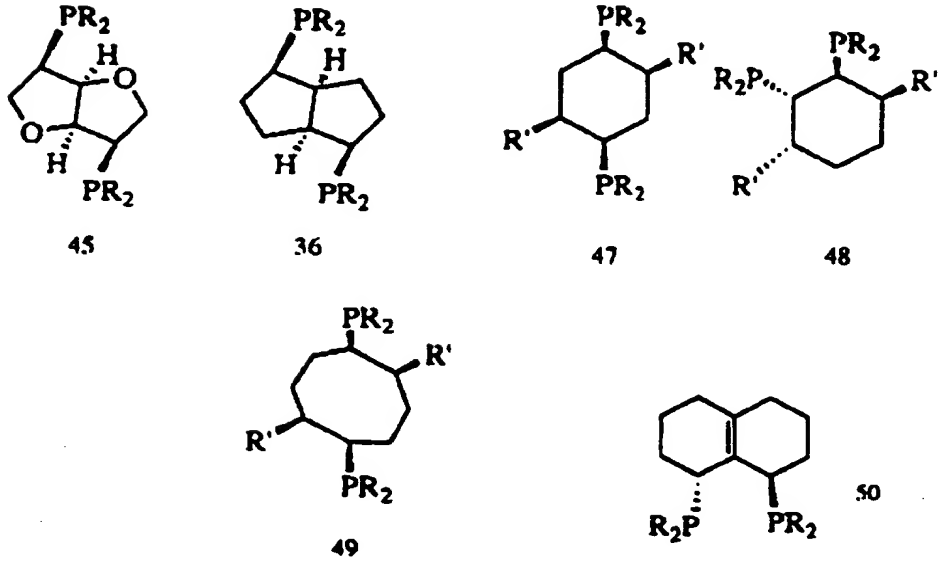
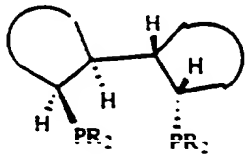


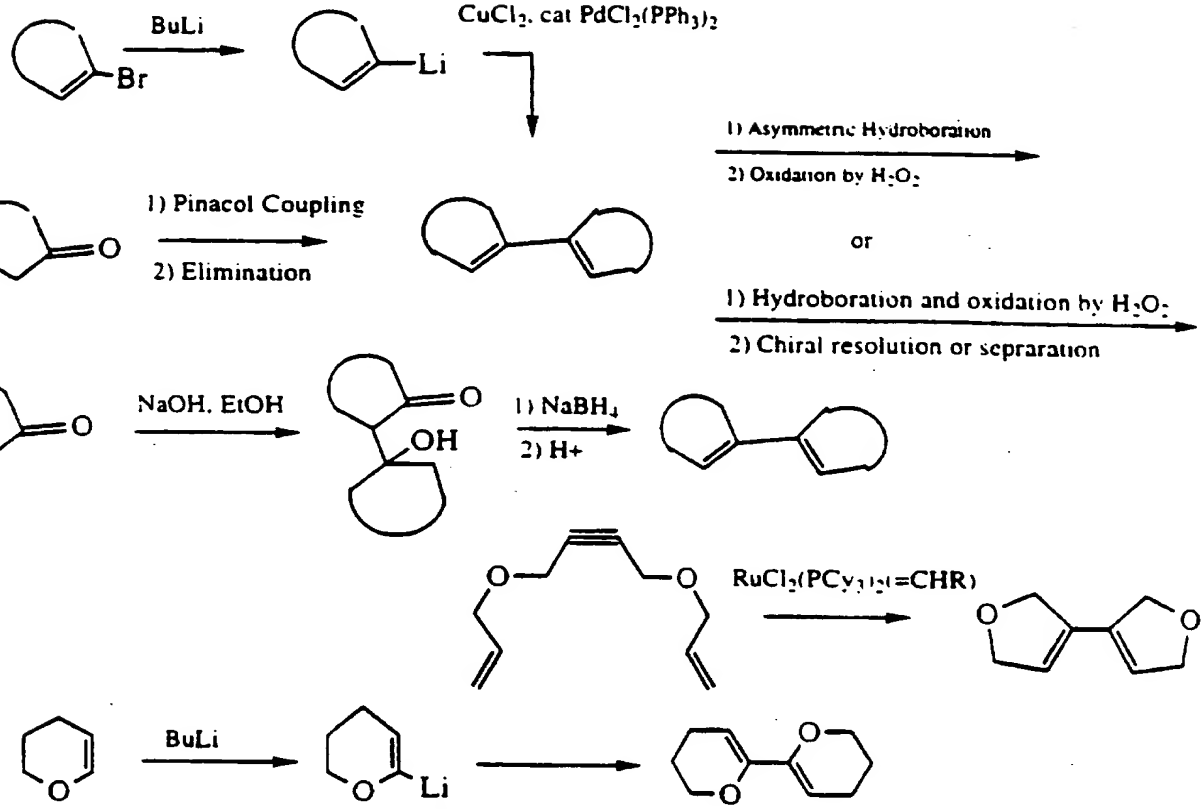
Figure 7. Selected new phosphine ligands with ring structures

Synthesis of Type I Bidentate Cyclic Phosphines

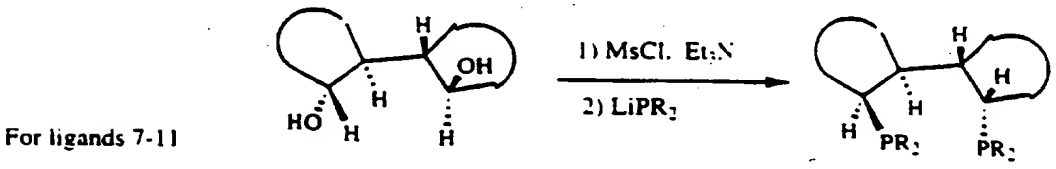


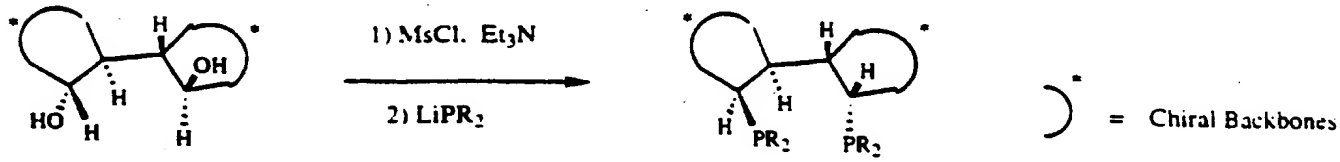
( ) = ring structure (ring size from 0 to 8) containing alkyl, aryl, heteroatoms or additional chiral centers

For ligands 1-6 and 12-13



For ligands 7-11





( )* = Chiral Backbones

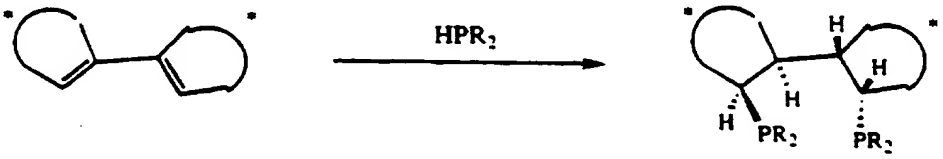


Figure 8

For ligands 7-11

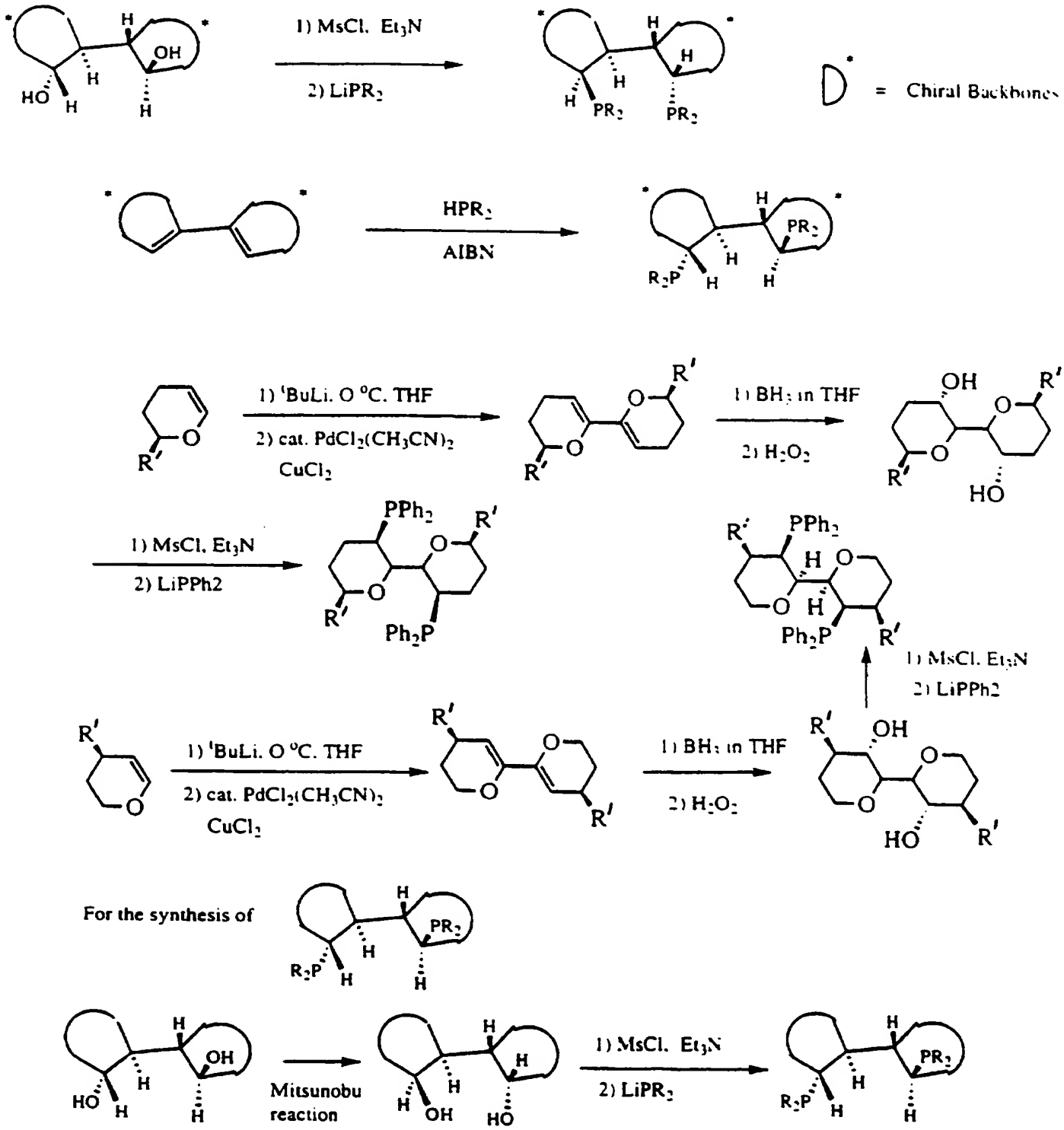


Figure 8 (Cont.)

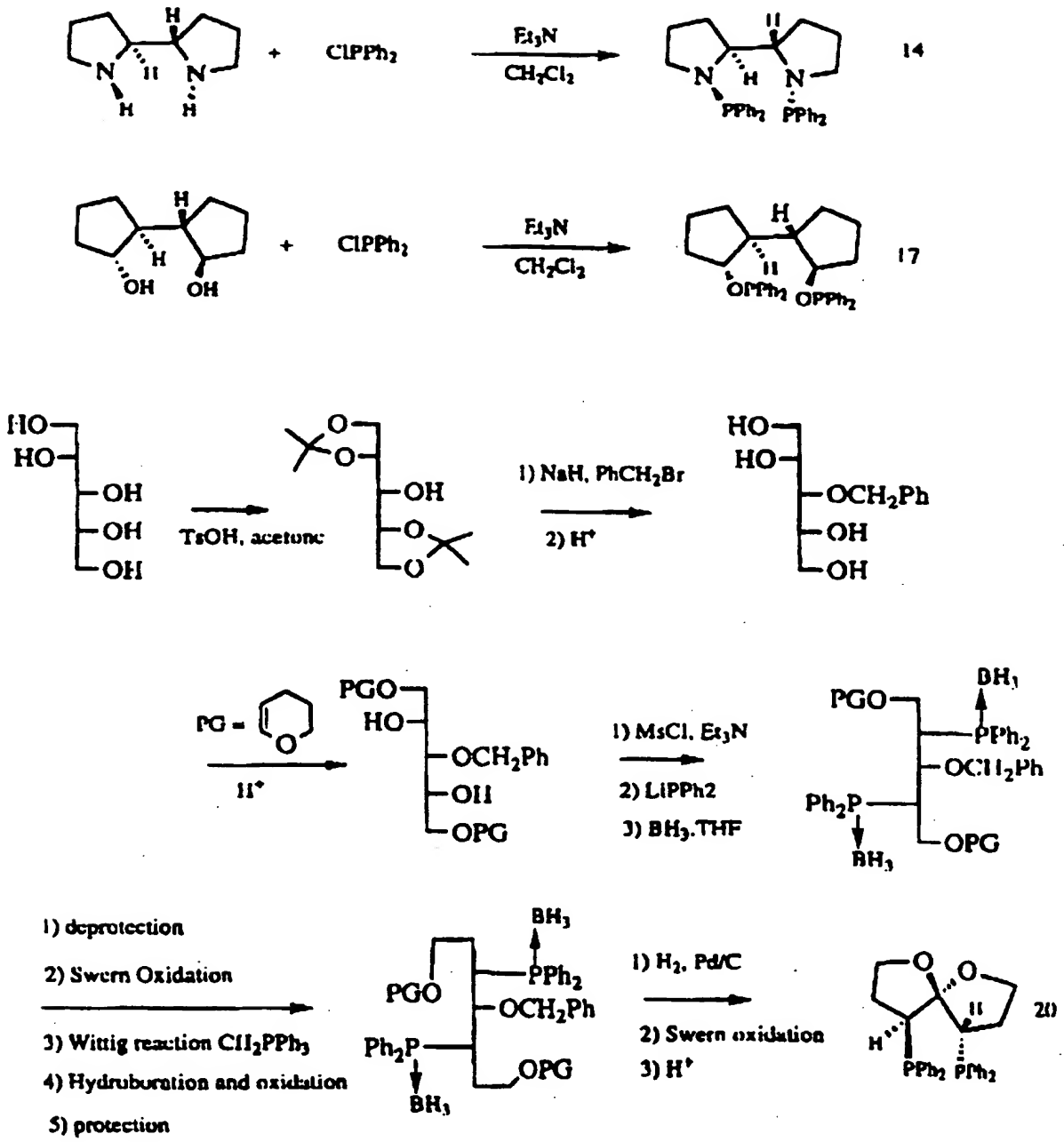
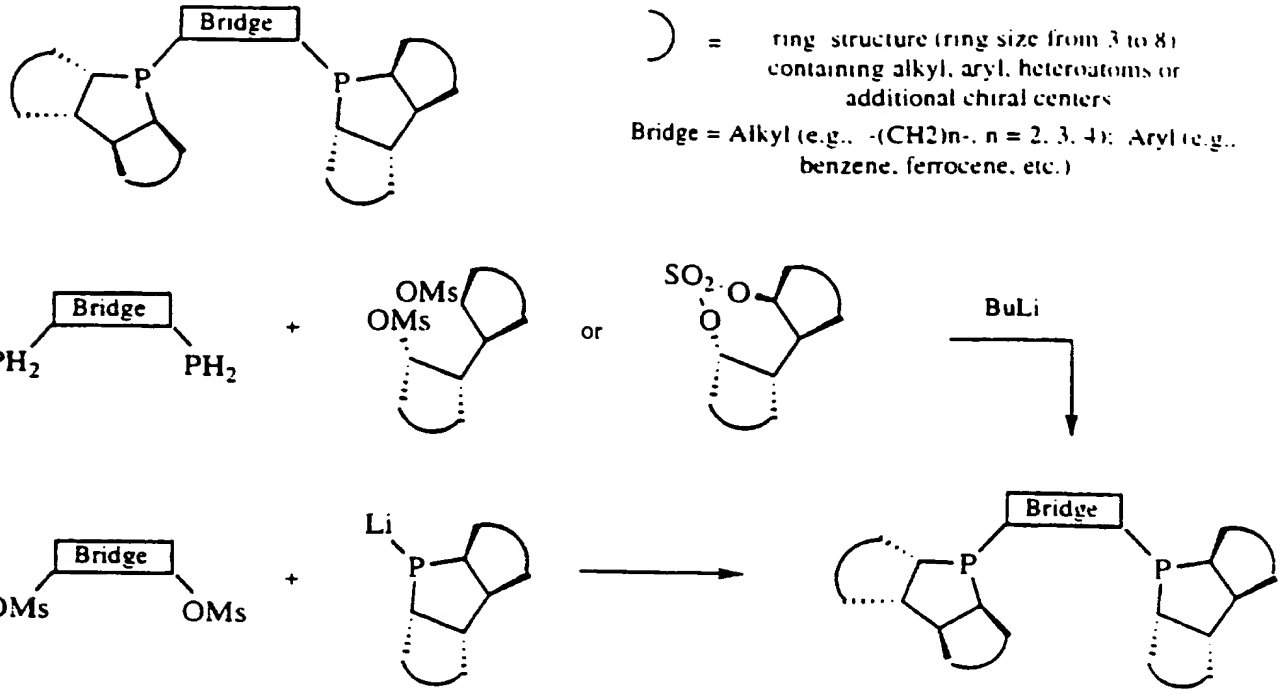
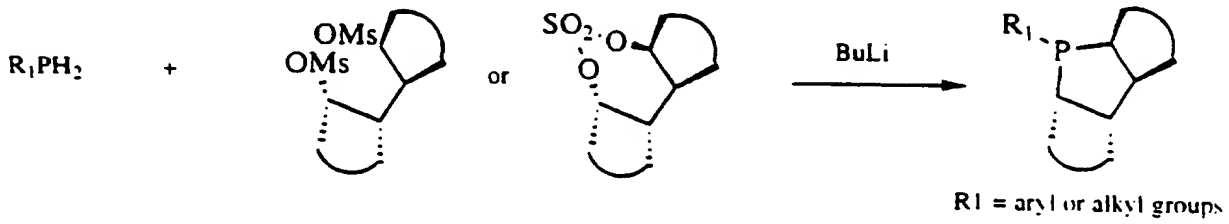


Figure 9. Synthesis of new chiral ligands 14-23.

Synthesis of Bidentate Cyclic Phosphines (Ligands 24-31)



Synthesis of Monodentate Chiral Phosphines (ligands 32-34)



R1 = aryl or alkyl groups

Figure 10

Figure 11 Synthesis of Bidentate Cyclic Phosphines (ligands 35-39)

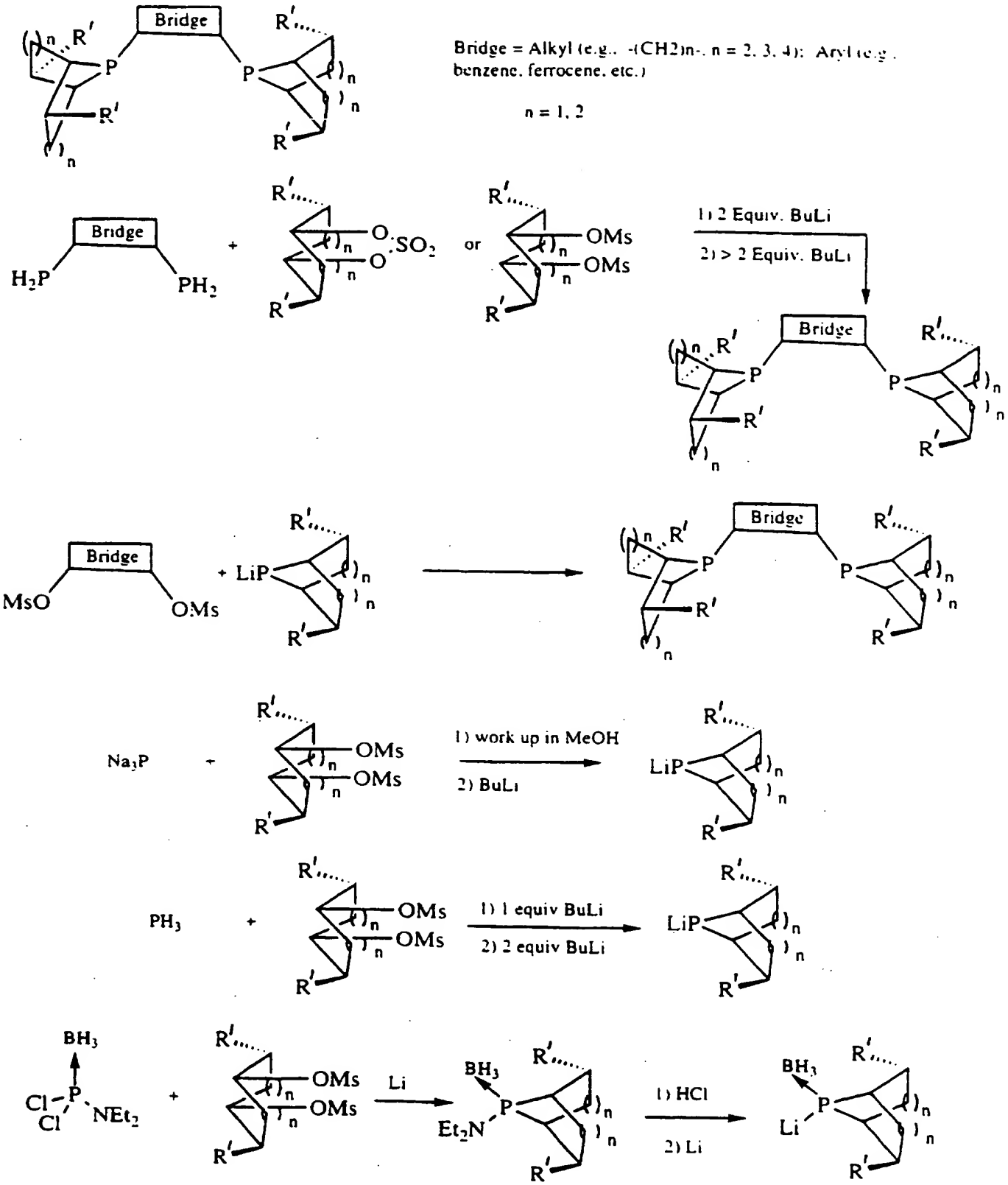
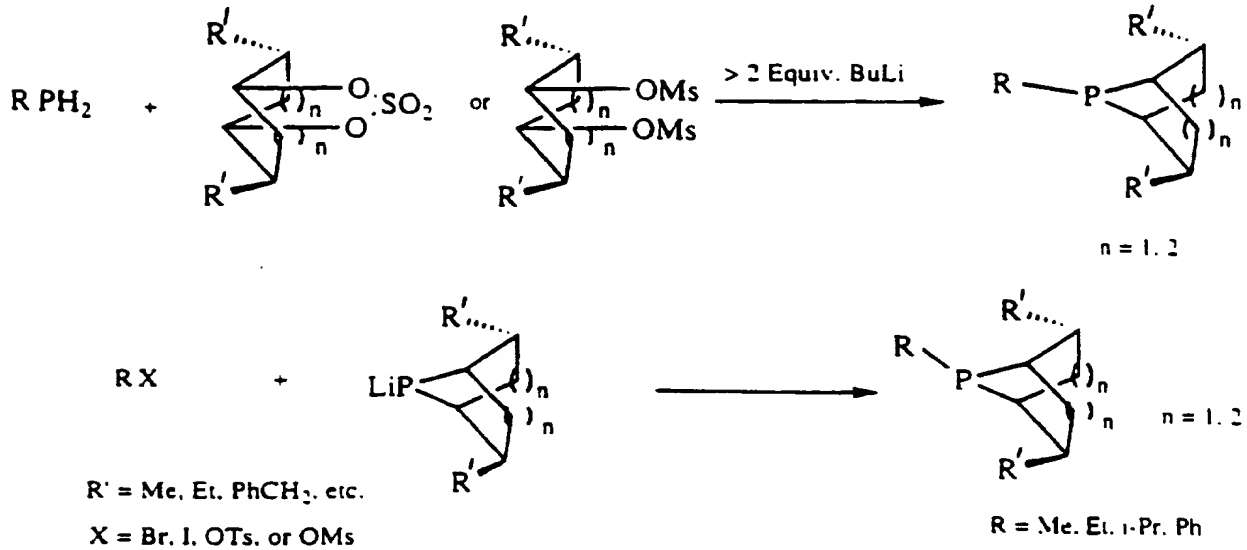


Figure 12 Synthesis of Bidentate Cyclic Phosphines (ligands 40-44)



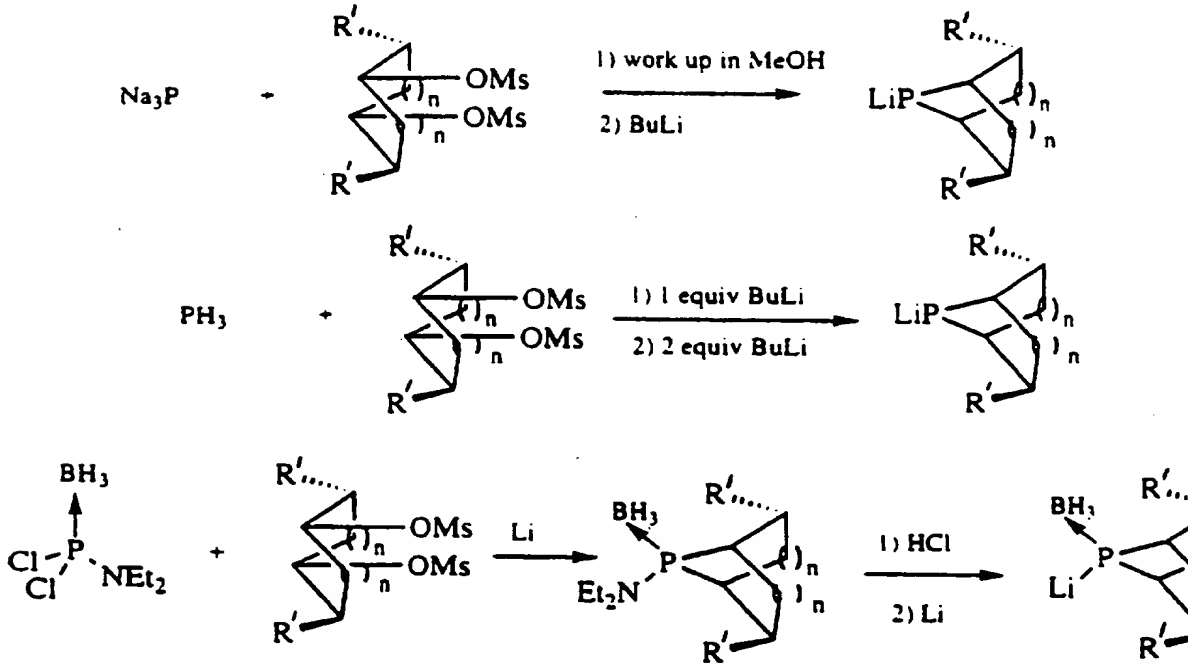


Figure 13. Synthesis of Bidentate Cyclic Phosphines (Ligands 45-49)

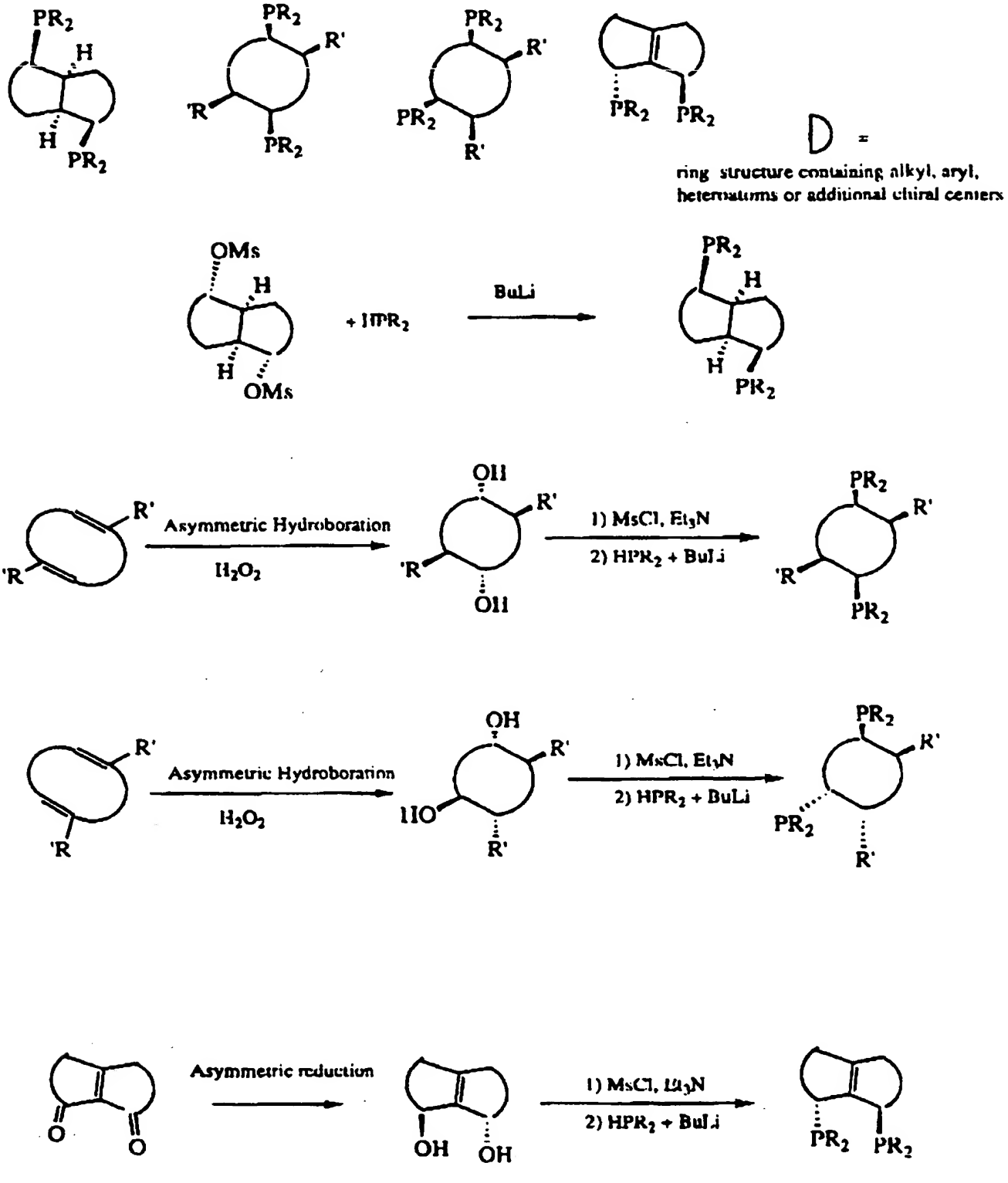
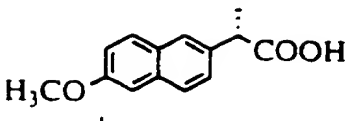
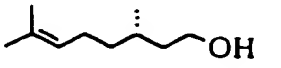


Figure 1 Some Applications of Asymmetric Catalytic Reactions

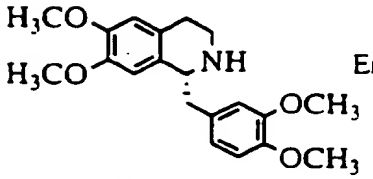


Naproxen — Antiinflammatory Agent

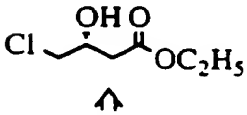


(S)-Citronellol — Fragrance

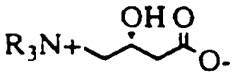
Intermediate — Synthesis of Prostanglandins



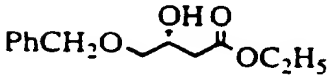
Enamide hydrogenation — Synthesis of isoquinoline alkaloids, Morphine, Benzomorphans, Dextromorphans



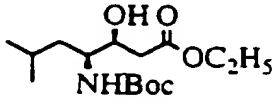
R = CH_3 — Carnitine, Transport of long-chain fatty acids through membranes



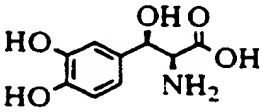
R = H — GABOB, an anti-epilepic and hypotensive drug



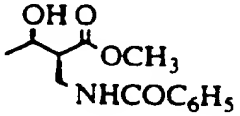
Intermediate — Compactin, a human menopausal gonadotropin-coenzyme A redutase inhibitor



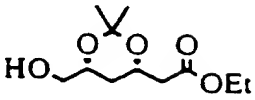
a protected statine, aspartic proteinase inhibitor

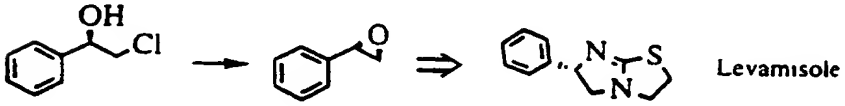


L-DOPS — an anti-Parkinsonian agent



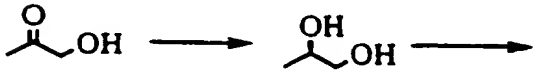
Intermediate — Antibiotic carbapenems



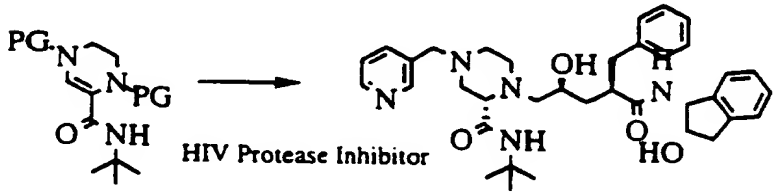


Levamisole

Daiso Technology



Levofloxacin



HIV Protease Inhibitor

Merck - Indinavir

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US97/10436

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :C07F 9/50, 9/28; C07D 331/02, 331/04, 333/46

US CL : 568/12, 14, 17; 546/21, 24; 549/5, 9, 13, 216

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 568/12, 14, 17; 546/21, 24; 549/5, 9, 13, 216

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

Please See Extra Sheet.

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	CHEN et al. Synthesis of Novel Chiral 2,5-Dialkyl-7-phosphabicyclo[2.2.1]heptanes, and Their Application in Highly Enantioselective Pd-Catalyzed Allylic Alkylations. J. Org. Chem. June 1997, Vol. 62, pages 4521-4523, see entire document.	1, 13-15, 18-20, 24-25, 28

[X] Further documents are listed in the continuation of Box C. [ ] See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"B"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
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Date of the actual completion of the international search

03 OCTOBER 1997

Date of mailing of the international search report

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US97/10436

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	Database Casplus on STN, Chemical Abstractsm(Columbus Ohio, USA), GELLING,O.J. 'Preparation of acetals by catalytic hydroformylation of alkenes,' abstract, WO9506025, March 1995, see entire document.	1, 16,18
A	OKADA et al. The First Synthesis of Chiral Phosphinocarboxylic AcidLigands,Trans-2-(Diphenylphosphino) Cycloalkanecarboxylic Acids. The Phosphine-Palladium Complexes Catalyzed Asymmetric Allylic Alkylation.Tetra. Lett. July 1990, Vol.31, No.27, pages 3905-3908.	1, 7-10, 13-18
A, P	US 5,596,114 A (BURK) 21 January 1997.	1, 7-10, 13-18
A	US 5,258,553 A (BURK) 02 November 1993.	1, 7-10, 13-18
A	US 5,426,223 A (BURK) 20 June 1995.	1, 7-10, 13-18
A	US 5,177,230 A (BURK) 05 January 1993.	1, 7-10, 13-18
A	US 5,008,457 A (BURK) 16 April 1991.	1, 7-10, 13-18
A	US 3,105,096 A (WELCHER) 24 September 1963.	1, 7-10, 13-18

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US97/10436

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.: 2-8 AND 11-12
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

The claims recite the limitation of "D" as a ring structure however the figures in the claims do not have a D drawn within them.

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☒ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☒ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US97/10436

B. FIELDS SEARCHED
Electronic data bases consulted (Name of data base and where practicable terms used):

APS, CAS ONLINE, BEILSTEIN, GMELIN
search terms: hydroformylation, phosphine, phosphinite, catalyst, chiral, bridged phosphines, platinum group metals, Diels Alder, hydrocarboxylation, Heck reaction, rhodium phosphines, platinum phosphines, also did structure drawning search on each different intermediate group.

CORRECTED VERSION*

PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

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A1

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60/033,493	20 December 1996 (20.12.96)	US
Not furnished	9 May 1997 (09.05.97)	US

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(54) Title: ASYMMETRIC SYNTHESIS CATALYZED BY TRANSITION METAL COMPLEXES WITH CYCLIC CHIRAL PHOSPHINE LIGANDS

(57) Abstract

The present invention relates to rigid chiral ligands useful in making catalysts for asymmetric synthesis. More particularly, the present invention relates to new monodentate and bidentate cyclic chiral phosphine ligands which are formed into catalysts to provide high selectivity of the enantiometric structure of the end-product.

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Asymmetric Synthesis Catalyzed by Transition Metal Complexes with Cyclic Chiral Phosphine Ligands

This application claims priority to the following U.S. provisional applications: 60/019,938 filed on June 14, 1996; 60/033,493 filed on December 20, 1996; and 60/____ filed on May 9, 1997.

Technical Field of the Invention

The present invention relates to rigid chiral ligands useful in making catalysts for asymmetric synthesis. More particularly, the present invention relates to new monodentate and bidentate cyclic chiral phosphine ligands which are formed into catalysts to provide high selectivity of the enantiomeric structure of the end-product.

Background of the Invention

The biological activities of many pharmaceuticals, fragrances, food additives and agrochemicals are often associated with their absolute molecular configuration. While one enantiomer gives a desired biological function through interactions with natural binding sites, another enantiomer usually does not have the same function and sometimes has deleterious side effects. A growing demand in pharmaceutical industries is to market a chiral drug in enantiomerically pure form. To meet this challenge, chemists have explored many approaches for acquiring enantiomerically pure compounds ranging from optical resolution and structural modification of naturally occurring chiral substances to asymmetric catalysis using synthetic chiral catalysts and enzymes. Among these methods, asymmetric catalysis is often the most efficient because a small amount of a chiral catalyst can be used to produce a large quantity of a chiral target molecule. During the last two decades, great effort has been devoted to discovering new asymmetric catalysts and more than a half-dozen commercial industrial processes have used asymmetric catalysis as the key step in the production of enantiomerically pure compounds.[1]

Asymmetric phosphine ligands have played a significant role in the development of novel transition metal catalyzed asymmetric reactions. Over 1000 chiral diphosphines[2]

have been made since the application of the DIPAMP ligand[3] for the industrial production of L-Dopa, yet only a few of these ligands afford the efficiency and selectivity required for commercial applications. Among these ligands, BINAP is one of the most frequently used bidentate chiral phosphines. The axially dissymmetric, fully aromatic BINAP ligand has been demonstrated to be highly effective for many asymmetric reactions. Duphos and related ligands have also shown high enantioselectivities in numerous reactions. However, there are a variety of reactions in which only modest enantioselectivity has been achieved with these ligands. Highly selective chiral ligands are needed to facilitate asymmetric reactions.

Figure 1 lists known chiral bidentate phosphines (DIPAMP,[3] BPPM,[4] DEGPHOS,[5] DIOP,[6] Chiraphos,[7] Skewphos,[8] BINAP,[9] Duphos,[10] and BPE[10]). While high selectivities were observed in many reactions using some of these chiral diphosphine ligands, there are many reactions where these ligands are not very efficient in terms of activity and selectivity. There are many disadvantages associated with these ligands, which hinder their applications. For DIPAMP, the phosphine chiral center is difficult to make. This ligand is only useful for asymmetric hydrogenation reaction. For BPPM, DIOP and Skewphos, the methylene group in the ligands causes conformational flexibility and enantioselectivities are moderate for many catalytic asymmetric reaction. DEGPHOS and CHIRAPHOS coordinate transition metal in five-membered ring. The chiral environment created by the phenyl groups is not close to the substrates and enantioselectivities are moderate. BINAP, DuPhos and BPE ligands are good for many asymmetric reactions. However, the rotation of aryl-aryl bond makes BINAP very flexible. The flexibility is an inherent limitation in the use of phosphine ligands. Furthermore, because the BINAP contains three aryl groups, it is less electron donating than phosphines that have less aryl groups. This is an important factor which influences reaction rates. For hydrogenation reactions, electron donating phosphines are more active. For the more electron donating DUPHOS and PBE ligands, the five membered ring adjacent to the phosphines is flexible.

U.S. Patents 5,329,015; 5,386,061; 5,532,395 describe phosphines prepared through chiral 1, 4-diols. These patents also describe divalent aryl and ferrocene bridging groups. U.S. Patent 5,258,553 describes chiral tridentate ligand phosphine ligands. The

above ligands are made into Group VIII transitional catalyst and are used to conduct enantioselective catalytic reactions such as asymmetric hydrogenation of olefins, ketones and imines. These references illustrate the preparation of catalyst from phosphine ligands and the conducting of various asymmetric synthesis. These patent disclosures are incorporated herein by reference.

The present invention discloses several new bidentate and monodentate phosphine ligands for asymmetric catalysis. The common feature of these ligands are that they contain rigid ring structures useful for restricting conformational flexibility of the ligands, thus enhancing chiral recognition. The present invention provides families of chiral diphosphines by variation of the steric and electronic environments (i.e., change of P-M-P bite angles and substituents on phosphine). In such a manner, the present invention provides an efficient and economical method with which to synthesize chiral drugs and agrochemicals.

Brief Description Of The Figures

Figure 1 list known chiral bidentate phosphines. While high selectivities were obtained in many reactions using some of these chiral diphosphine ligands, there are many reactions where these ligands are not very efficienct in terms of activity and selectivity. There are many disadvantages associated with these ligands, which hinder their applications. For DIPAMP, the phosphine chiral center is difficult to make. This ligand is only useful for limited application in asymmetric hydrogenation. For BPPM, DIOP, and Skewphos, the methylene group in the ligands causes conformational flexibility and enantioselectivities are moderate for many catalytic asymmetric reactions. DEGPHOS and CHIRAPHOS coordinate transition metals in five-membered ring. The Chiral environment created by the phenyl groups is not close to the substrates and enantionselectivities are moderate for many reactions. BINAP, DuPhos and BPE ligands are good for many asymmetric reactions. However, the rotation if aryl-aryl bond makes BINAP very flexible. The flexibility is an inherent limitation in the use of phosphine ligand. Furthermore, because the phosphine of BINAP contains adjacent three aryl groups , it is less electron donating than phosphine that have less aryl groups. This is an important factor which influences reaction rates. For hydrogenation reactions, electron

donating phosphines are more active. For the more electron donating DUPHOS and BPE ligands, the five-membered ring adjacent to the phsophines is flexible.

Figure 2 illustrates ligands 1-13 (Type I). These ligands have at less four chiral centers in their backbones and they can form seven-membered chelating ring with many transition metals. The two cyclic rings in the backbone limit the conformational flexibility. The two carbon stereogenic centers adjacent to PR_2 may be inverted as illustrated in Figure 2.

Figure 3 depicts ligands 14-23. Ligands 14-16 (Type II) have a nitrogen-phosphine bond in the ligands. Ligands 17-19 (Type III) have many phosphine-oxygen bonds. Ligands 20-23 (Type IV) have spiro-ring structure in their backbones. These ligands can be regarded as derivatives of ligands 1-13 with structure variation of their backbones.

Figure 4 depicts ligands 24-34 (Type V), chiral phosphines with phospha-tricyclic structures.

Figure 5 and 6 illustrate type VI chiral phosphines with fused phospha-bicyclic structures.

Figure 7 shows type VII chiral phosphine ligands having one or two rings in their backbones.

Figure 8 outlines the synthesis of the type I ligands, 1-13. Asymmetric hydroboration of dienes or hydroboration of chiral dienes can lead to chiral 1,4-diols. Chiral resolution of diols can also provide an effective routes to chiral diols. Dienes and chiral dienes may be generated using variety of methods including but not limited to Pinacol coupling and elimination, aldol condensation followed by reduction and elimination, Methathesis, and coupling of vinyl halide or vinyl lithium. Mesylation of diols and nucleophilic attack of mesylates with a variety of phosphides can produce the desired products. With chiral dienes, the free-radical addition of HPR_2 may lead to the products. For the inversion of the chiral diol, Mitsunobo reaction may be applied.

Figure 9 illustrates the synthesis of ligands 14-23. For the chiral ligands containing P-O or P-N bonds, the corresponding chiral diols or chiral diamines are presented. For the spiro phosphines, one pathway is to construct spiro-structure in the

last step. This is because direct nucleophilic attack by $LiPPh_2$ to the corresponding spiro dimesylate is difficult due to the steric hinderance of adjacent carbon group.

Figure 10 describes the synthesis of phospha-tricyclic compounds from the corresponding diols.

Figure 11 and 12 describes the synthesis of chiral fused phospha-bicyclic compounds. A typical procedure uses $RPLi_2$ as nucleophiles. However, phospha-bicyclic anion can be made and nucleophilic attack with bridge groups (XRX or RX where R is alkyl or aryl and X is a halide, tosylate or mesylate) by this anion can generate the desired ligands.

Figure 13 outlines the synthetic procedures for ligands 45 to 50.

Figure 14 illustrates applications of asymmetric catalytic reactions.

Summary Of The Invention

It is an objective of the present invention to provide a chiral diphosphine ligand that provides high enantioselectivity and activity. The present invention therefore provides a chiral phosphine ligand having a conformationally rigid cyclic structure, in which the phosphorus may be bonded to or be part of the cyclic structure. As such, the ligand rigidity provides enhanced chiral discrimination in metal catalyzed asymmetric organic reactions. In one embodiment, a "type I" or "type II" chiral bidentate phosphine ligand having a 2,2'-bis(diorganophosphino)-1,1'-bis(cyclic) structure wherein each cycle of the bis(cyclic) structure comprises 3 to 8 carbon atoms wherein the 1, 1', 2 and 2' carbon atoms in the bis(cyclic) structure are saturated carbon atoms and wherein the carbon atoms in the bis(cyclic) structure other than the 1, 1', 2 and 2' carbon atoms are optionally replaced with a heteroatom including but not limited to nitrogen, oxygen or sulfur; and wherein type II ligands have nitrogen in the 2,2' position, is provided.

In another embodiment, a "type III" chiral bidentate phosphine ligand having a 1,1'-bis(cyclic)-2,2'(organophosphinite) structure is provided.

In yet another embodiment, a "type IV" chiral phosphine ligand having a heteroatom-containing sprio bis-organophosphine or organophosphinite is provided.

In one embodiment, a "type V" chiral bidentate phosphine ligand having a (bis)phospha-tricyclic structure with a bridge group is provided.

In another embodiment, a "type VI" chiral phosphine ligand having a (bis)fused phospha-bicyclic structure comprising a bridge structure is provided.

In yet another embodiment, a "type VIIa" chiral phosphine ligand having a cis(bis) phosphine fused bicyclic structure is provided.

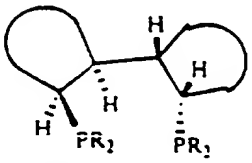
In one embodiment, a "type VIIb" chiral phosphine ligand having a cis or trans biphosphine cyclic structure having two R' substituents where R' is alkyl, fluoroalkyl or perfluoroalkyl (each having up to 8 carbon atoms), aryl, substituted aryl, arylalkyl, ring-substituted arylalkyl, and $-CR'_2(CR'_2)_qZ(CR'_2)_pR'$ where q and p are the same or different integers ranging from 1 to 8 and Z is defined as O, S, NR, PR, AsR, SbR, divalent aryl, divalent fused aryl, divalent 5-membered ring heterocyclic group, or a divalent fused heterocyclic group where R is alkyl of 1-8 carbon atoms, aryl, or substituted aryl is provided. In another embodiment, a "type VIIc" chiral phosphine ligand having a trans(bis) phosphine bicyclic structure.

In yet another embodiment, a "type V" chiral monodentate phosphine ligand comprising a phospha-tricyclic structure is provided.

And, in yet another embodiment, a "type VI" chiral monodentate phosphine ligand comprising a phospha-bicyclic structure is provided.

And, in yet another embodiment, a cyclic phosphine ligand having a structure of :

A. Bidentate cyclic chiral phosphines:



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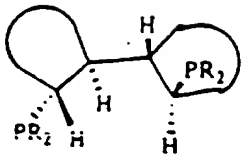

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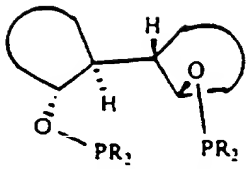

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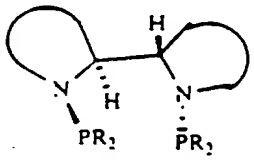

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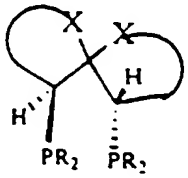
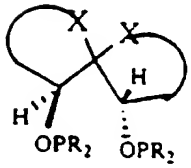


Type IV



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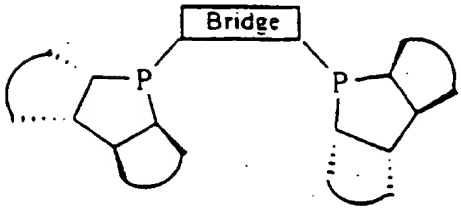

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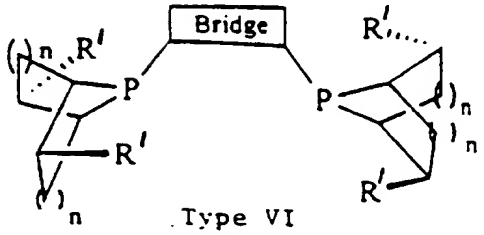

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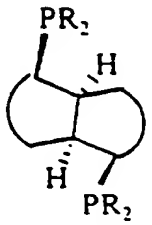

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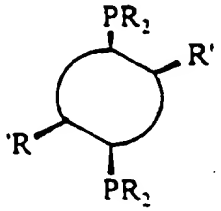

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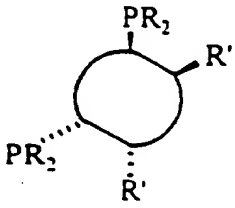

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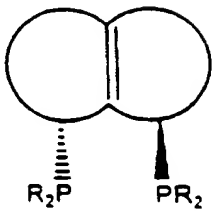
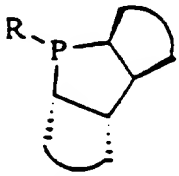


Type VIIc

or

B. monodentate cyclic chiral phosphines



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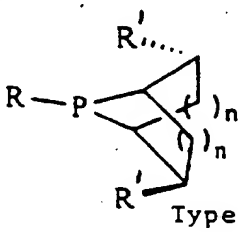


Type VI

where each R is independently alkyl of 1-8 carbon atoms, substituted alkyl, aryl, or substituted aryl; each R' is independently alkyl, fluoroalkyl and perfluoroalkyl, each having up to 8 carbon atoms; aryl; substituted aryl; arylalkyl; ring-substituted arylalkyl; and $-CR'_2(CR'_2)_qZ(CR'_2)_pR'$ wherein q and p are the same or different integers ranging

from 1 to 8, R' is as defined above, and Z is selected from the group consisting of O, S, NR, PR, AsR, SbR, divalent aryl, divalent fused aryl, divalent 5-membered ring heterocyclic group, and a divalent fused heterocyclic group where R is as defined above; the cyclic structure D represents a ring having 3 to 8 carbon atoms which may be substituted within the ring with one or more oxygen, sulfur, N-R', C=O, or CR'_2; D represents 0 to 8 carbon atoms; and where the ring may further be substituted with R' as defined above; the Bridge is $-(CH_2)_r-$ where r is an integer ranging from 1 to 8; $-(CH_2)_sZ(CH_2)_m-$ wherein s and m are each the same or different integers ranging from 1 to 8; 1,2-divalent phenyl; 2,2'divalent-1,1'biphenyl; 2,2'divalent 1,2'binapthyl; and ferrocene; each of which may be substituted with R' as defined above; and where the substitution on 1,2-divalent phenyl, the ferrocene or biaryl bridge is independently hydrogen, halogen, alkyl, alkoxyl, aryl, aryloxy, nitro, amino, vinyl, substituted vinyl, alkynyl, or sulfonic acid; X is O, S or NR where R is as defined above; and n is 1 or 2.

It is yet another objective of the present invention to provide a catalyst that provides high enantioselectivity and activity; in one embodiment of the present invention, a chiral phosphine ligand as described above complexed with a transition metal, preferably rhodium, iridium, ruthenium, palladium or platinium is provided.

In certain compounds of the present invention, the phosphine ligand is attached to an organic substrate or backbone by a chemical bridging group or organic substituent. For these compounds, it is preferred that the chemical bridging group or organic substituent has a linker to a polymer. The polymer-supported catalyst is a heterogenous or homogenous catalyst, dependent upon the solubility of the polymer in the reaction medium.

It is another objective of the present invention to provide a method for transition metal complex catalyzed asymmetric hydrogenation of ketones, imines, or olefin; in one embodiment, a method is provided in which such a reaction is catalyzed by a chiral phosphine ligand as described above complexed with a transition metal, preferably rhodium, iridium, ruthenium, palladium or platinium is provided.

It is yet another objective of the present invention to provide an improved method for a transition metal catalyzed asymmetric reaction such as hydrogenation, hydride transfer reaction, hydrosilylation, hydroboration, hydrovinylation, hydroformylation,

hydrocarboxylation, allylic alkylation, cyclopropanation, Diels-Alder reaction, Aldol reaction, Heck reaction, Michael addition, and stereo-selective polymerization in one embodiment, the improvement comprising catalysing the reaction with a catalyst that is a chiral phosphine ligand as described above complexed with a transition metal, preferably rhodium, iridium, ruthenium, palladium or platinium. In yet another embodiment, the catalyst is selected from the group consisting of compound 1 as illustrated in Figure 1, compound 36 as illustrated in Figure 5, compound 40 as illustrated in Figure 6, and compound 26 as illustrated in Figure 4. In another embodiment, the catalyst is a complex of a chiral phosphine complexed with a compound that is $[Rh(COD)Cl]_2$, $[Rh(COD)_2]X$ (X = BF_4, ClO_4, SbF_6, CF_3SO_3), $[Ir(COD)Cl]_2$, $[Ir(COD)_2]X$ (X = BF_4, ClO_4, SbF_6, CF_3SO_3,), $Ru(COD)Cl_2$, $[Pd(CH_3CN)_4[BF_4]_2$, $Pd_2(dba)_3$, and $[Pd(C_3H_5)Cl]_2$. And, in yet another embodiment, the catalyst is $Ru(RCOO)_2(Y)$, $RuX_2(Y)$, $Ru(methylallyl)_2(Y)$, $Ru(aryl\ group)X_2(Y)$, where where X is Cl, Br or I and Y is a chiral diphosphine of the present invention.

It is yet another objective of the present invention to provide an improved method for asymmetric hydration of a ketone, imine or olefin catalyzed by a complex comprising Ru, Rh and Ir and a chiral ligand; in one embodiment, the improvement includes conducting the catalysis with a palladium complex having a chiral phosphine ligand as described above. In yet another embodiment, the catalyst is selected from the group consisting of compound 1 as illustrated in Figure 1, compound 36 as illustrated in Figure 5, and compound 26 as illustrated in Figure 4.

It is another method of the present invention to provide an improved method for asymmetric allyllic alkylation catalyzed by a complex comprising palladium and a chiral ligand; in one embodiment, the improvement includes catalysis with a palladium complex having a chiral ligand as described above. In yet another embodiment, the catalyst includes compound 40 as illustrated in Figure 6.

It is yet another objective of the present invention to provide an intermediate for synthesis of a chiral phosphine ligand. In one embodiment, the intermediate shown as compound 3 in Scheme 2 is provided.

NR, PR, AsR, SbR, divalent aryl, divalent fused aryl, divalent 5-membered ring heterocyclic group, and a divalent fused heterocyclic group where R is as defined above; the cyclic structure D represents a ring having 3 to 8 carbon atoms which may be substituted within the ring with one or more oxygen, sulfur, N-R', C=O, or CR'_2; D represents 0 to 8 carbon atoms; and where the ring may further be substituted with R' as defined above; the Bridge is $-(CH_2)_r-$ where r is an integer ranging from 1 to 8; $-(CH_2)_sZ(CH_2)_m-$ wherein s and m are each the same or different integers ranging from 1 to 8; 1,2-divalent phenyl; 2,2'divalent-1,1'biphenyl; 2,2'divalent 1,2'binapthyl; and ferrocene; each of which may be substituted with R' as defined above; and where the substitution on 1,2-divalent phenyl, the ferrocene or biaryl bridge is independently hydrogen, halogen, alkyl, alkoxyl, aryl, aryloxy, nitro, amino, vinyl, substituted vinyl, alkynyl, or sulfonic acid; X is O, S or NR where R is as defined above; and n is 1 or 2.

It is yet another objective of the present invention to provide a catalyst that provides high enantioselectivity and activity; in one embodiment of the present invention, a chiral phosphine ligand as described above complexed with a transition metal, preferably rhodium, iridium, ruthenium, palladium or platinium is provided.

In certain compounds of the present invention, the phosphine ligand is attached to an organic substrate or backbone by a chemical bridging group or organic substituent. For these compounds, it is preferred that the chemical bridging group or organic substituent has a linker to a polymer. The polymer-supported catalyst is a heterogenous or homogenous catalyst, dependent upon the solubility of the polymer in the reaction medium.

It is another objective of the present invention to provide a method for transition metal complex catalyzed asymmetric hydrogenation of ketones, imines, or olefin; in one embodiment, a method is provided in which such a reaction is catalyzed by a chiral phosphine ligand as described above complexed with a transition metal, preferably rhodium, iridium, ruthenium, palladium or platinium is provided.

It is yet another objective of the present invention to provide an improved method for a transition metal catalyzed asymmetric reaction such as hydrogenation, hydride transfer reaction, hydrosilylation, hydroboration, hydrovinylation, hydroformylation, hydrocarboxylation, allylic alkylation, cyclopropanation, Diels-Alder reaction, Aldol

reaction, Heck reaction, Michael addition, and stereo-selective polymerization in one embodiment, the improvement comprising catalysing the reaction with a catalyst that is a chiral phosphine ligand as described above complexed with a transition metal, preferably rhodium, iridium, ruthenium, palladium or platinium. In yet another embodiment, the catalyst is selected from the group consisting of compound 1 as illustrated in Figure 1, compound 36 as illustrated in Figure 5, compound 40 as illustrated in Figure 6, and compound 26 as illustrated in Figure 4. In another embodiment, the catalyst is a complex of a chiral phosphine complexed with a compound that is $[Rh(COD)Cl]_2$, $[Rh(COD)_2]X$ ($X = BF_4$, ClO_4, SbF_6, CF_3SO_3), $[Ir(COD)Cl]_2$, $[Ir(COD)_2]X$ ($X = BF_4$, ClO_4, SbF_6, CF_3SO_3,), $Ru(COD)Cl_2$, $[Pd(CH_3CN)_4[BF_4]_2$, $Pd_2(dba)_3$ and $[Pd(C_3H_5)Cl]_2$. And, in yet another embodiment, the catalyst is $Ru(RCOO)_2(Y)$, $RuX_2(Y)$, Ru(methylallyl)$_2$(Y), Ru(aryl group)X_2(Y), where where X is Cl, Br or I and Y is a chiral diphosphine of the present invention.

It is yet another objective of the present invention to provide an improved method for asymmetric hydration of a ketone, imine or olefin catalyzed by a complex comprising Ru, Rh and Ir and a chiral ligand; in one embodiment, the improvement includes conducting the catalysis with a palladium complex having a chiral phosphine ligand as described above. In yet another embodiment, the catalyst is selected from the group consisting of compound 1 as illustrated in Figure 1, compound 36 as illustrated in Figure 5, and compound 26 as illustrated in Figure 4.

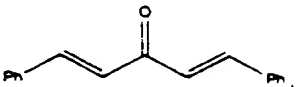
It is another method of the present invention to provide an improved method for asymmetric allyllic alkylation catalyzed by a complex comprising palladium and a chiral ligand; in one embodiment, the improvement includes catalysis with a palladium complex having a chiral ligand as described above. In yet another embodiment, the catalyst includes compound 40 as illustrated in Figure 6.

It is yet another objective of the present invention to provide an intermediate for synthesis of a chiral phosphine ligand. In one embodiment, the intermediate shown as compound 3 in Scheme 2 is provided.

Detailed Description

In the description of the cyclic chiral phosphine ligands above the term aryl includes phenyl, furan, thiophene, pyridine, pyrole, napthyl and similar aromatic rings. Substituted aryl and substituted vinyl refer to an aryl or vinyl, respectively, substituted with one or more alkyl groups having 1-8 carbon atoms, alkoxy having 1-8 carbon atoms, alkylcarbonyl having 1-8 carbon atoms, carboxy, alkoxycarbonyl having 2-8 carbon atoms, halo (Cl, Br, F or I) amino, alkylamino or dialkylamino.

An suitable aryl, divalent aryl or divalent fused aryl for use in the present invention includes but is not limited to those derived from the parent compound benzene, anthracene or fluorene. A suitable 5-membered ring heterocyclic group for use herein includes but is not limited to one derived from the parent heterocyclic compound furan, thiophene, pyrrole, tetrahydrofuran, tetrahydrothiopene, pyrrolidine, arsole or phosphole. A suitable fused heterocyclic group for use herein includes but is not limited to one derived from the parent compound bipyridine, carbazole, benzofuran, indole, benzpyrazole, benzopyran, benzopyronone or benzodiazine. A suitable aryloxy group for use in the present invention includes but is not limited to an aryl having an oxygen atom as a substituent.

"dba" is defined as  .

"COD" is defined as  .

Alkyls having 1-8 carbon atoms includes straight or branched chain alkyls and cycloalkyls having 3 to 8 carbon atoms. Representative examples are methyl, ethyl, propyl, isopropyl, butyl, tertiary butyl, pentyl, cyclopentyl, hexyl cyclohexyl and the like. The alkyl group may be substituted with phenyl, substituted phenyl or alkoxy, carboxy, alkyoxycarbonyl, halo, amino, or alkyl amino or dialkylamino as defined above.

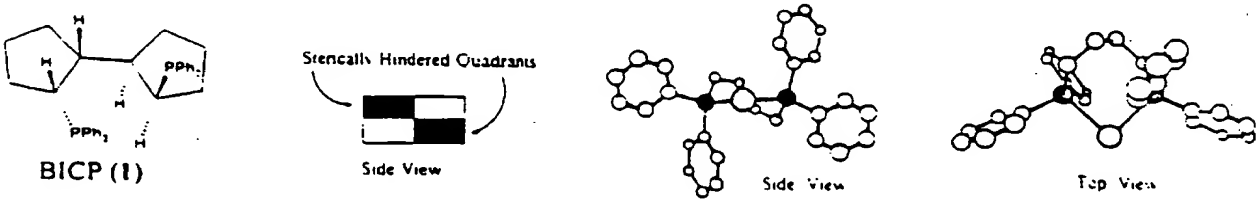
Certain compounds of the present invention provide a phosphine ligand attached to an organic substrate or backbone. In such cases, the chemical bridging group or the allyl or akyl groups adjacent to phosphine may include a linker to a polymer; the polymer supported-catalyst is a heterogenous or homogenous catalyst dependent upon the solubility of the polymer in the reaction medium.

Those skilled in the chemical art will recognize a wide variety of equivalent substituents.

The cyclic chiral phosphine ligands of the present invention are reacted with transistion metals to form catalyst. Preferably Group VIII transition metals are used and most preferably the catalyst is formed with rhodium, iridium, ruthenium, or palladium.

The invention encompasses a variety of asymmetric reactions utilizing catalyst of the invention, such as hydrogenation, hydride transfer, hydrosilylation, Grignard Cross-coupling, hydrocyanation, isomerisation, cycloadditions, Sigmatropic rearrangement, hydroboration, hydroformylation, hydrocarboxylation, allylic alkylation, hydrovinylation, cyclopropanation, aldol reaction, Heck reaction, Michael addition, and stereo-selective polymerization can be carried out with these ligand systems. The catalyst of this invention provides efficient and practical methods for producing chiral drugs for antihypertensive, antihistamine, cardiovascular and central nervous system therapies. The transition metal complexes of cyclic chiral phosphine ligands of the present invention are also important in the production of chiral agrochemicals.

The invention is illustrated by the synthesis and application of a chiral 1,4-bisphosphine, (2R, 2'R)-bis(diphenylphosphino)-(1R, 1'R)-dicyclopentane (1) (abbreviated (R, R)-BICP) (Scheme 2) in the rhodium catalyzed asymmetric hydrogenation of α-(acylamino)acrylic acids. An important feature of this ligand is that it contains two cyclopentane rings in its backbone which are present to restrict its conformational flexibility leading to high enantioselectivity in asymmetric reactions.

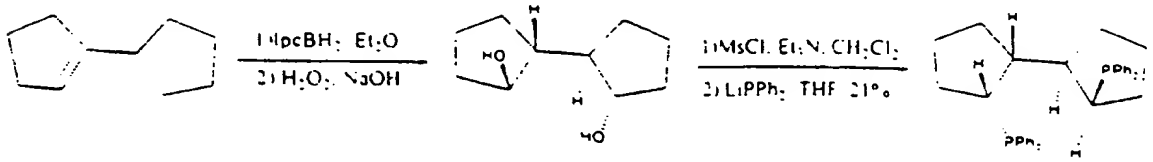


BICP (1)

Scheme 1

The bisphosphine ligand (1, R, R-BICP) was synthesized from readily available 1,1'-dicyclopentene (2)[11] as shown in Scheme 1. Asymmetric hydroboration of 2 using

(−)-monoisopinocamphenylborane [(−) IpcBH2] followed by oxidation with H_2O_2[12] gave the desired chiral diol (3) (100% ee after recrystallization from ether/hexanes), which was then converted to the dimesylate in high yield. Subsequent reaction of the dimesylate with lithium diphenylphospine afforded the bisphosphine 1.



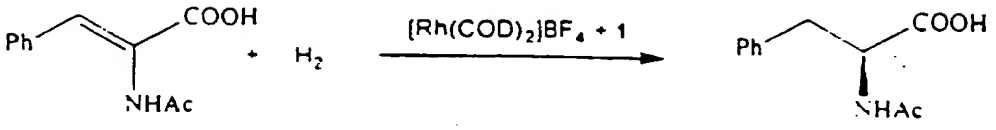
2 3 R, R- BICP 1

Scheme 2

Hydrogenation of α-acetoamidocinnamic acid was carried out at rt and 1 atm of hydrogen in the presence of the catalyst formed *in situ* from [Rh(COD)2]BF4 and bisphosphine 1 (1:1.1). Table 1 shows the results of hydrogenation of α-acetoamidocinnamic acid under a variety of conditions. The addition of a catalytic amount of triethylamine (Rh:1:Et3N=1:1.1:50) gave a better optical yield than without triethylamine (Entry 1 vs 2). This effect may be due to a conformational change in the chiral Rh complex, since the carboxylate anion generated from the substrate and triethylamine has a greater affinity for the metal than the corresponding acid.[9a] The enantioselectivity in the hydrogenation was found to be highly dependent on the nature of the Rh complex. When a neutral Rh complex was used as the catalyst precursor, the optical yield decreased dramatically (entry 3). The highest selectivity (96.8%, *S*) for the hydrogenation of α-acetoamidocinnamic acid was obtained in THF at 1 atm of H_2 in the presence of triethylamine (entry 4), while changing substrate.catalyst ratio had a small effect on the enantioselectivities (entry 4 vs 5).

TABLE 1

Optimization of the asymmetric hydrogenation of α-acetamidocinnamic acid[a]



Entry	Solvent	Et_3N (%)	ee (%)[b]
1	EtOH	---	89.2
2	EtOH	50	93.3
3[c]	EtOH	50	83.6
4	$ClCH_2CH_2Cl$	50	93.4
5	THF	50	96.8
6[d]	THF	5	95.1

a. The reaction was carried out at rt under 1 atm of H_2 for 24 h [substrate (0.5 mmol, 0.125 M):$[Rh(COD)_2]BF_4$:ligand(1) = 1:0.01:0.011]. The reaction went in quantitative yield.

b. Determined by GC using aChirasil-VAL III FSOT column on the corresponding methyl ester. The S absolute configuration was determined by comparing the optical rotation with the reported value.

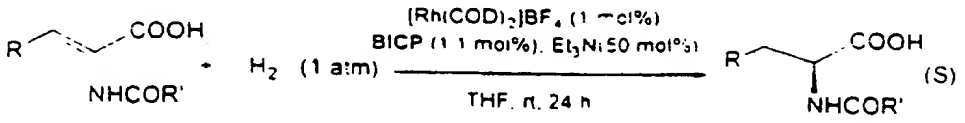
c. 0.5 mol% $[Rh(COD)Cl]_2$ was used as the catalyst precursor.

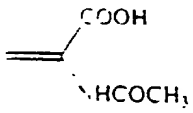
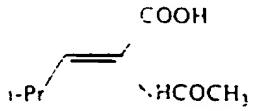
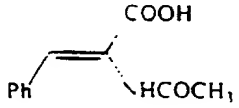
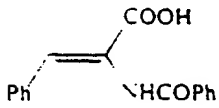
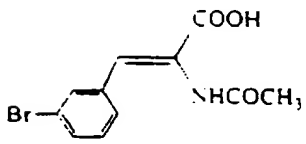
d. 0.1mol % $[Rh(COD)_2]BF_4$/0.11mol% ligand (1)/5 mol% Et_3N were used.

The metholology is useful in the asymmetric synthesis of chiral amino acids. Tables 2 and 3 show the enantioselectivity of some amino acids obtained by hydrogenation of α-(acylamino)acrylic acids under an optimum condition. Enantioselectivities in this hydrogenation were not sensitive to the substitution pattern on the β-position of the prochiral olefin substrates, where α-benzamidocinnamic acid gave better optical yields than the corresponding acetoamido derivative.

TABLE 2

Asymmetric Hydrogenations of Dehydroamino Acid Derivatives

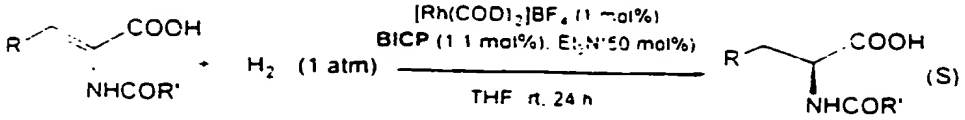


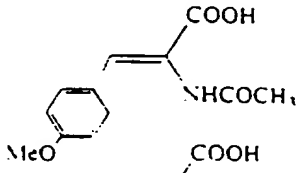
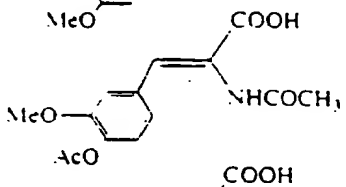
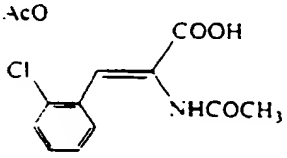
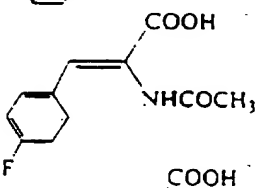
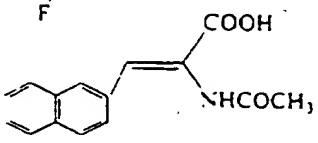
Entry	Substrate	Con. %	% ee[a]
1		100	97.5
2		100	92.6
3		100	96.8
4		100	99.0
5		100	97.0

a. % ee determined by GC using Chirasil-VAL III FSOT Column of the corresponding methyl ester.

TABLE 3

Asymmetric Hydrogenations of Dehydroamino Acid Derivatives



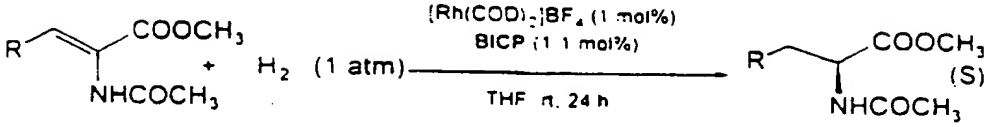
Entry	Substrate	Con. %	% ee[a]
6		100	99.0
7		100	98.2
8		100	92.5
9		100	91.6
10		100	92.9

a. % ee determined by GC using Chirasil-VAL III FSOT Column of the corresponding methyl ester or by HPLC (OJ collumn)

For the corresponding methyl ester, the results are summarized in Table 4.

TABLE 4

Asymmetric Hydrogenations of Methyl Ester of Dehydroamino Acid Derivatives



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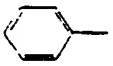
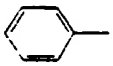
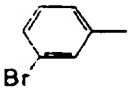
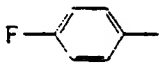
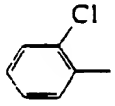
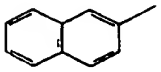
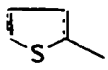
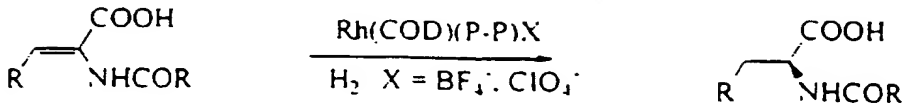
2		100	78.4
3[b]		100	60.0
4		100	75.1
5		100	80.5
6		100	70.9
7		100	85.3
8		100	79.1

a. % ee determined by GC using Chirasil-VAL III FSOT Column
b. 50mol% Et_3N was added

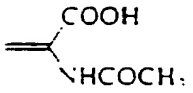
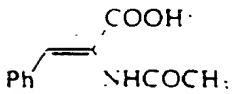
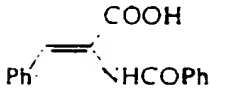
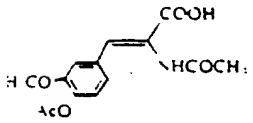
Table 5 illustrates comparative asymmetric hydrogenations of dehydroamino acid derivatives.

TABLE 5

Asymmetric Hydrogenations of Dehydroamino Acid Derivatives



P-P = chiral diphenylphosphine (% ee)

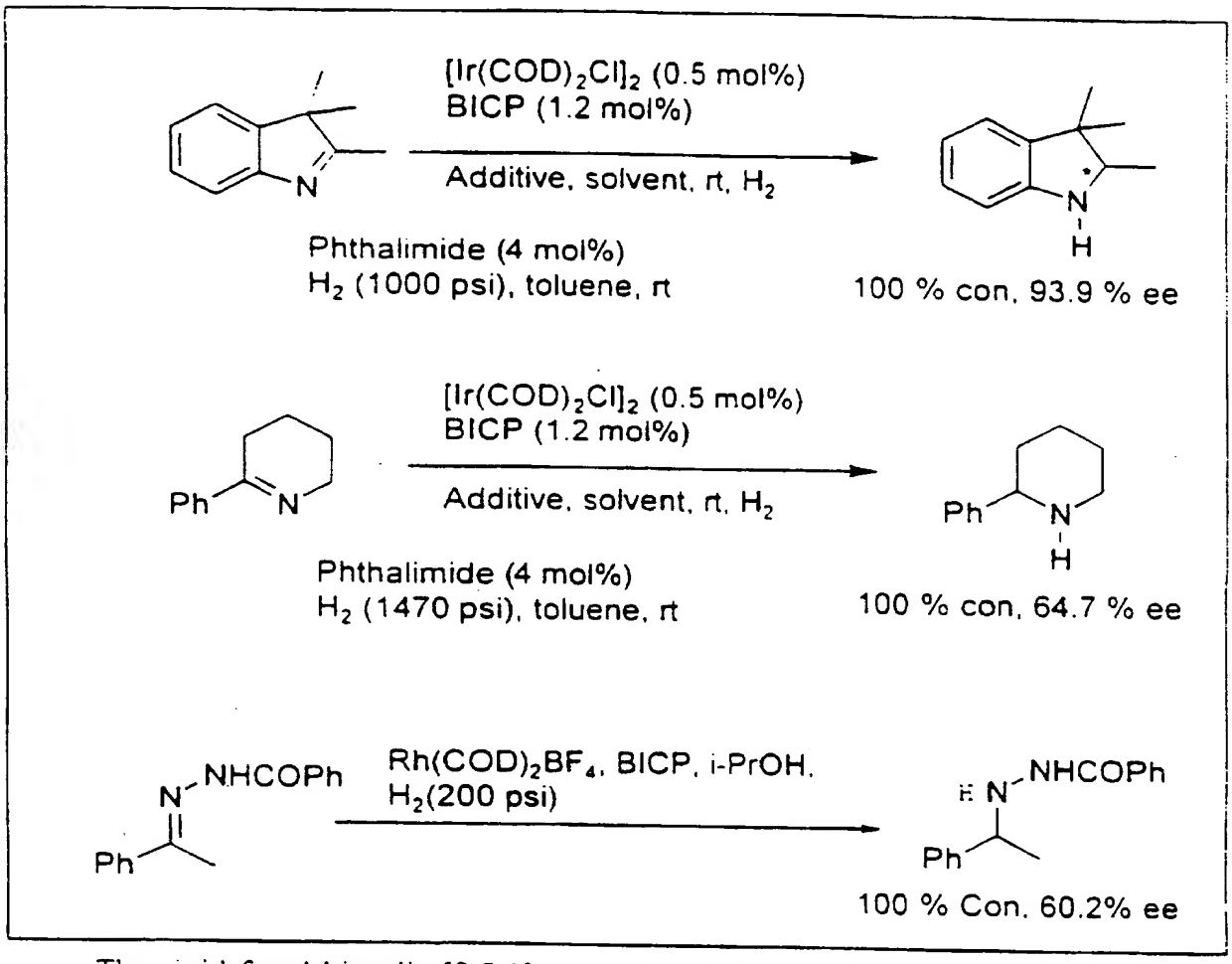
Substrate	DiPAMP	BINAP	CHIRAPHOS	BPPM	DIOP	BICP
	94	67	91	**98**	73	**98**
	95	84	89	91	81	**97**
	96	**100**	**99**	83	64	**99**
	94	79*	83	86	84	**98**

* NHCOPh

For the asymmetric hydrogenation of imines, rhodium iridium-complexes of BICP are effective. Table 6 provides some results on this asymmetric reaction. For an imine substrate, up to 94 % ee has achieved and this is among the highest enantioselectivity obtained with group VIII transition metal catalysts coordinated by a chiral phosphine ligand.

TABLE 6

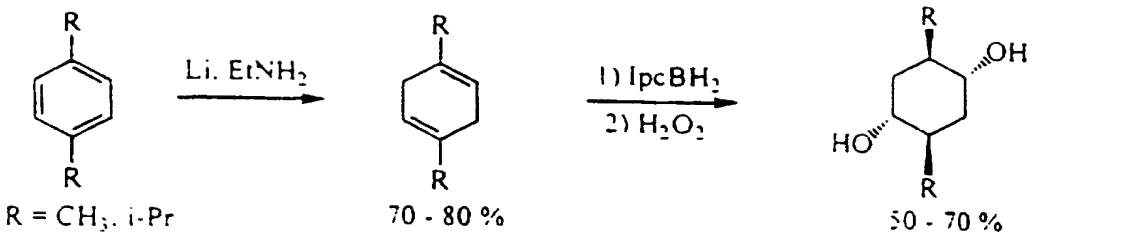
Ir and Rh-Catalyzed Asymmetric Hydrogenation of Imines

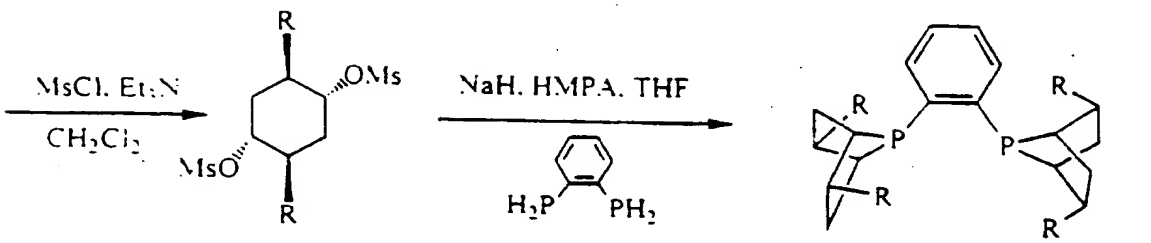


The rigid fused bicyclic [2.2.1] structure represents a new motif in chiral ligand design. Changes in the size of the R group on the ring system can modulate the asymmetric induction and high enantioselectivities can be achieved. Scheme 3 shows the synthesis of new chiral bicyclic phosphines (abbreviated as PennPhos because it represents a different structure from DuPhos [DuPont Phosphine] and was made at Penn State).

Scheme 3

Synthesis of PennPhos

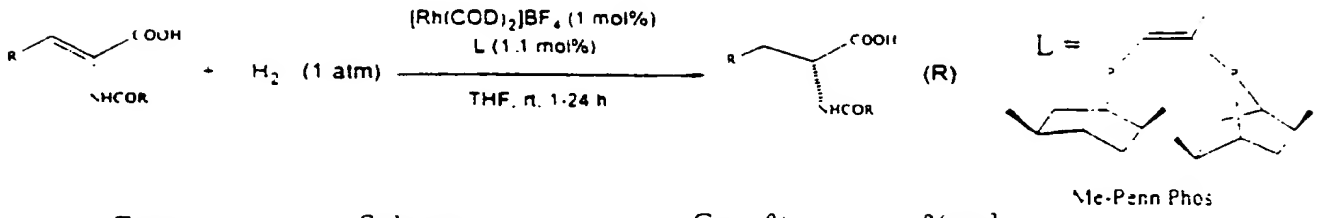


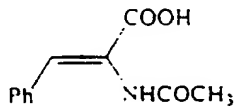
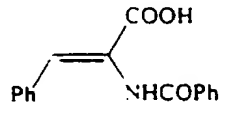
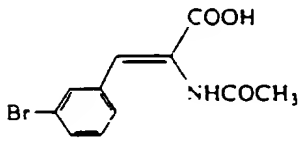
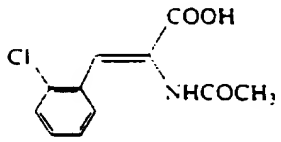
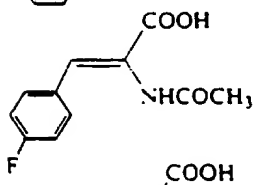
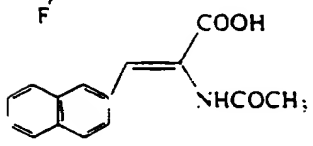


Rhodium complexes with PennPhos ligands can be used as catalyts for asymmetric hydrogenation. Table 7 lists the asymmetric hydrogenation results for dehydroamino acid derivatives.

TABLE 7

Asymmetric Hydrogenations of Dehydroamino Acid Derivatives



Entry	Substrate	Con. %	% ee[a]
1		100	84.3
2		100	52.8
3		100	82.7
4		100	82.3
5		100	81.9
6		100	83.5

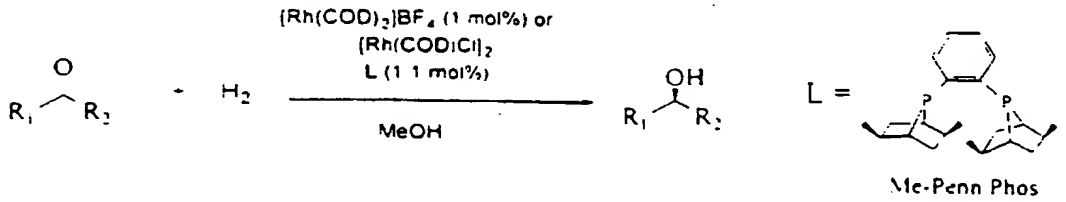
a. % ee determined by GC using Chirasil-VAL III FSOT Column of the corresponding methyl ester.

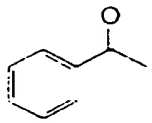
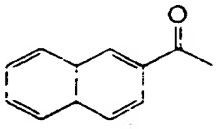
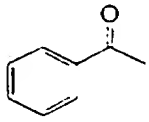
The rhodium complexes with Me-Pennphos are very effective for hydrogenation of simple ketones. Up to 97 % ee has been obtained with acetophenone, which is the

highest enantioselectivity reported in the direct asymmetric hydrogenation of simple ketones with group VIII transition metal complexes. Table 8 summarizes some results for this study.

TABLE 8

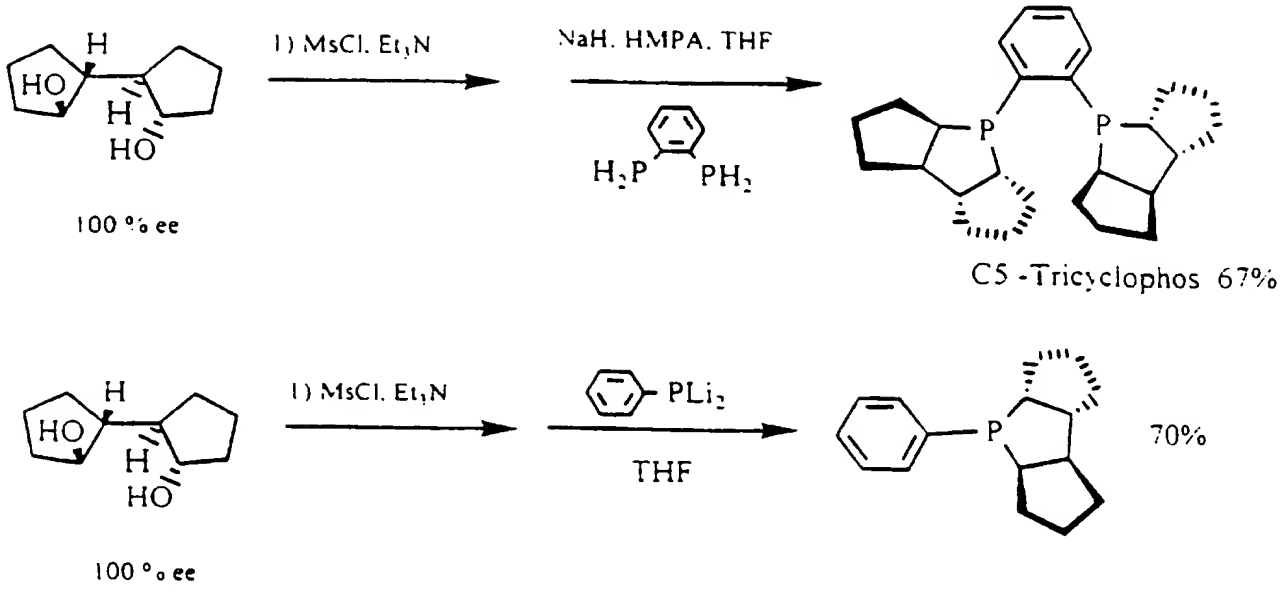
Asymmetric Hydrogenations of Simple Ketones



Entry	Substrate	Catalyst	H_2 Pressure	Con. %	% ee
1		$[Rh(COD)Cl]_2$	30 atm	97	96.5
2		$[Rh(COD)Cl]_2$	30 atm	70	91
3		$[Rh(COD)_2]BF_4$	70 atm	73	79.6

Synthesis of another chiral cyclic phosphines is illustrated in Scheme 4. The phospha-tricyclic structure is unique and the phosphines are made from chiral 1,4-diols with two rings. Tricyclic structure dictates the chiral environment around phosphines and ring size can be changed by varing the chiral diols. Both monophosphines and bisphosphines can be made from the straightforward synthetic route. They can be used as ligands for many asymmetric reactions.

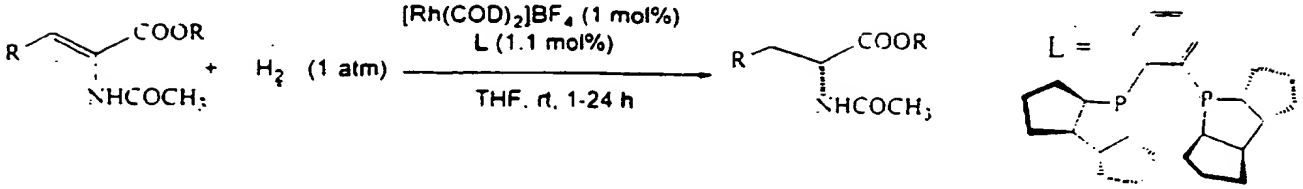
Scheme 4

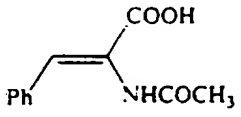
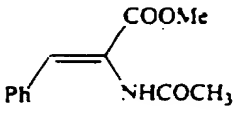


Rhodium complexes with these chiral tricyclic phosphines can be used as catalysts for asymmetric hydrogenation. Table 9 lists the asymmetric hydrogenation results for dehydroamino acid derivatives.

TABLE 9

Asymmetric Hydrogenations of Dehydroamino Acid Derivatives

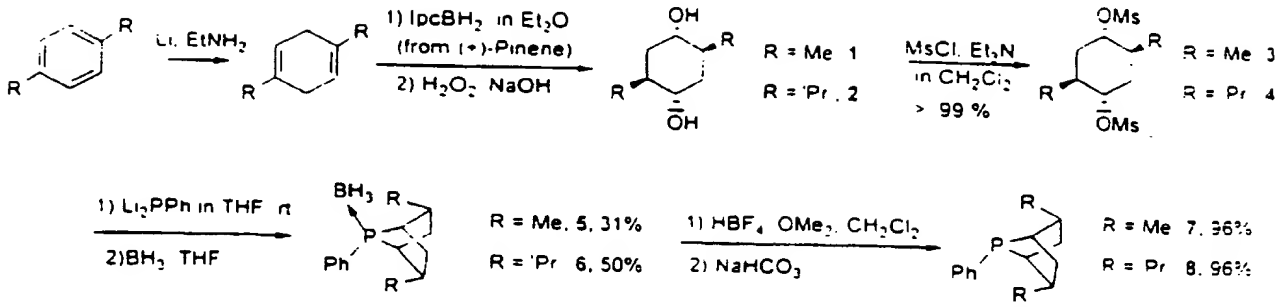


Entry	Substrate	Con. %	% ee[a]
1		100	52.9
2		100	77.6

a. % ee determined by GC using Chirasil-VAL III FSOT Column of the corresponding methyl ester.

The rigid fused bicyclic [2.2.1] structure represents a new motif in chiral ligand design. Analogous to Burk's systems, changes in the size of the R group on the ring system can modulate the asymmetric induction and high enantioselectivities can be achieved. The present invention provides the syntheses of chiral monophosphines with this fused bicyclic ring structure (Scheme 5) and their application in Pd-catalyzed asymmetric allylic alkylations.

SCHEME 5



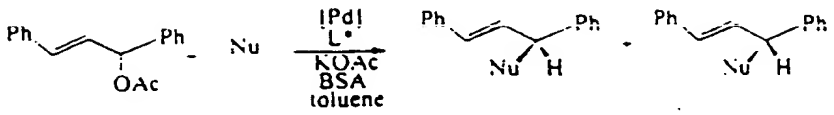
(40)

The ligand synthesis depends on the availability of enantiomerically pure cyclic 1,4-diols. Halterman[13] and Vollhardt[14] have previously prepared chiral cyclopentadiene derivatives from the chiral diols.[13-14] Halterman[13] has synthesized chiral diols 1 and 2 from the inexpensive starting materials *p*-xylene and *p*-diisopropylbenzene, respectively. The synthesis employed Birch reduction, followed by asymmetric hydroboration and recrystallization to 100 % ee. Conversion of the optically pure diols to the corresponding mesylates proceeds cleanly. Nucleophilic substitution by Li_2PPh on the chiral dimesylates 3 and 4 generated the corresponding bicyclic phosphines, which were trapped by BH_3•THF to form the air-stable boron-protected monophosphines 5 and 6, respectively. Deprotection with a strong acid produces the desired products [7, (1*R*, 2*S*, 4*R*, 5*S*)-(+)-2, 5-dimethyl-7-phenyl-7-phosphabicyclo[2.2.1]heptane; 8, (1*R*, 2*R*, 4*R*, 5*R*)-(+)-2, 5-diisopropyl-7-phenyl-7-phosphabicyclo-[2.2.1]heptane] in high yields.

Pd-catalyzed allylic alkylation was utilized to test the effectiveness of these new monophosphines as chiral ligands. Although many palladium complexes of multidentate phosphine and nitrogen ligands are excellent catalysts for this reaction,[15] palladium complexes of simple chiral monophosphines are normally not effective.[15] However, Pd-catalyzed allylic alkylation with the new monophosphine 7 gave excellent enantioselectivities and conversions (Table 10), comparable to the best results (99 % ee) reported to date.[15]

TABLE 10

Palladium-Catalyzed Asymmetric Allylic Alkylation with Chiral Monophosphines[a]



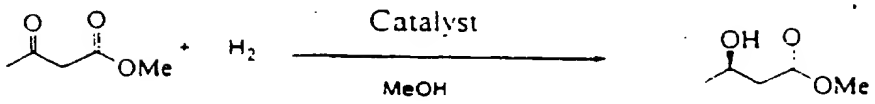
Entry	L*	[Pd]	[Pd] : L*	Nu	Additive	Time (h)	Yield (%)	% ee[b]
1	7	$Pd_2(dba)_3$	1 : 2.2	$CH_2(CO_2Me)_2$	–	1.5	96	74 (R)
2	7	$Pd(OAc)_2$	1 : 2.2	$CH_2(CO_2Me)_2$	–	4.0	98	72 (R)
3	7	$[Pd(C_3H_5)Cl]_2$	1 : 1.1	$CH_2(CO_2Me)_2$	–	5.0	97	60 (R)
4	7	$[Pd(C_3H_5)Cl]_2$	1 : 2.2	$CH_2(CO_2Me)_2$	–	2.0	93	95 (R)
5	7	$[Pd(C_3H_5)Cl]_2$	1 : 3.3	$CH_2(CO_2Me)_2$	–	1.5	96	96 (R)
6	7	$[Pd(C_3H_5)Cl]_2$	1 : 2.2	$CH_2(CO_2Me)_2$	2.8 % $AgBF_4$	1.0	80	97 (R)
7	7	$[Pd(C_3H_5)Cl]_2$	1 : 2.2	$CH_2(CO_2Me)_2$	2.8 % LiCl	2.0	95	96 (R)
8	7	$[Pd(C_3H_5)Cl]_2$	1 : 2.2	$CH_2(COMe)_2$	–	2.0	99	>97[c] (R)
9	7	$[Pd(C_3H_5)Cl]_2$	1 : 2.2	$CH(NHAc)(CO_2Et)_2$	–	2.0	95	>99.5[d] (S)
10	8	$[Pd(C_3H_5)Cl]_2$	1 : 2.2	$CH_2(CO_2Me)_2$	–	3.5	99	78 (R)

a The reaction was carried out under N_2 using 1,3-diphenyl-2-propenyl acetate, Nu (nucleophile) (300 mol%), BSA (bis(trimethylsilyl)acetamide) (300 mol%), KOAc (2 mol%), toluene, [Pd] 1.4 mol % and L*. b. % ee was measured by HPLC using a Chiralcel OD column, and the absolute configuration was determined by comparing the optical rotation with literature values. c. % ee was measured by comparing the optical rotation with literature values. d. % ee was measured by HPLC using a Chiracel OJ column.

Ruthenium complexes with chiral phosphines are excellent catalysts for the asymmetric hydrogenation of beta keto-esters. Table 11 lists the results based on Ru-BICP catalystic system.

TABLE 11

Asymmetric Hydrogenations of beta-Keto ester



Entry	Temp	Catalyst	H_2 Pressure	Con. %	% ee
1	65 °C	Ru(BICP)Br2	1 atm	97	82
2	40 °C	Ru(BICP)Br2	5 atm	95	76
3	50 °C	Ru(BICP)Cl2	5 atm	43	84

EXAMPLES

Unless otherwise indicated, all reactions were carried out under nitrogen. THF and ether were freshly distilled from sodium benzophenone ketyl. Toluene and 1,4-dioxane were freshly distilled from sodium. Dichloromethane and hexane were freshly distilled from CaH_2. Methanol was distilled from magnesium and CaH_2. Reactions were monitored by thin-layer chromatography (TLC) analysis. Column chromatography was performed using EM silica gel 60 (230-400 mesh). ^1H NMR were recorded on Bruker ACE 200, WP 200, AM 300 and WM 360 spectrometers. Chemical shifts are reported in ppm downfield from tetramethylsilane with the solvent resonance as the internal standard ($CDCl_3$, δ 7.26 ppm). ^{13}C, ^{31}P and ^1H NMR spectra were recorded on Bruker AM 300 and WM 360 or Varian 200 or 500 spectrometers with complete proton decoupling. Chemical shifts are reported in ppm downfield from tetramethylsilane with the solvent resonance as the internal standard ($CDCl_3$, δ 77.0 ppm). Optical rotation was obtained on a Perkin-Elmer 241 polarimeter. MS spectra were recorded on a KRATOS mass spectrometer MS 9/50 for LR-EI and HR-EI. GC analysis were carried on Helwett-Packard 5890 gas chromatograph with a 30-m Supelco β-DEX™ or r-225Dex™ column. HPLC analysis were carried on Waters™ 600 chromatograph with a 25-cm CHIRALCEL OD column.

Example 1

(as depicted in Scheme 2 and Figure 8)

(1R, 1'R)-Bicyclopentyl-(2S, 2'S)-diol (3 in scheme 2)

Compound 3 was synthesized by asymmetric hydroboration of bi-1-cyclopenten-1yl using (+)-monoisopinocampheylborane ((+)-IpcBH$_2$) according to the literature procedure (Brown, H. C.; Jadhav, P. K., Mandal, A. K. *J. Org. Chem.* **1982**, *47*, 5074). The absolute configuration of the diol was assigned based on the asymmetric hydroboration of trisubstituted olefins (e.g. methylcyclopentene) using (+)-IpcBH$_2$. ^1H NMR ($CDCl_3$, 300 MHz) δ 4.04(br, 2 H), 3.84 (m, 2 H), 2.02 (m, 2 H), 1.66-1.22 (m, 10 H), 1.21 (m, 2 H); ^{13}C NMR δ 78.6, 52.2, 33.6, 29.2, 20.5; MS m/z 170 (M^+, 0.35), 152, 134, 108 , 95, 84, 68; HRMS calcd for $C_{10}H_{18}O_2$: 170.1307(M^+); found: 170.1315.

Example 2

(as depicted in Scheme 2 and Figure 8)

(1R,1'R)-Bicyclopentyl-(2S,2'S)-diol bis(methanesulfonate)

To a solution of (1R, 1'R)-bicyclopentyl-(2S, 2'S)-diol (0.8 g, 4.65 mmol) and triethylamine (1.68 mL, 12.09 mmol) in CH_2Cl_2 (30 mL) was added dropwise a solution of methanesulfonyl chloride (0.76 mL, 9.92 mmol) in CH_2Cl_2 (2 mL) at 0°C. The reaction mixture was stirred at 0°C for 30 min. and at rt for 2 h, then quenched by saturated aqueous ammonium chloride solution (25 mL). The aqueous layer was extracted with CH_2Cl_2 (3x20 mL) and the combined organic solution was dried over Na_2SO_4. After evaporation of the solvent, a white solid was obtained, which was used directly for the next step. ^1H NMR ($CDCl_3$, 200 MHz) δ 5.01(m, 2H), 3.04 (s, 6 H), 2.17 (m, 2 H), 2.15-1.65 (m, 10 H), 1.43-1.52 (m, 2 H); ^{13}C NMR δ 86.8, 48.2, 38.4, 32.8, 27.4, 22.5.

Example 3

(as depicted in Scheme 2 and Figure 8)

(1R, 1'R, 2R, 2'R)-1,1'-Bis(2-diphenylphosphino)cyclopentyl bisborane

Diphenylphosphine (1.25 mL, 7.0 mmol) in THF (80 mL) was cooled to -78°C. To this solution, n-BuLi in hexane (4.1 mL, 6.6 mmol) was added via syringe over 5 min. The resulting orange solution was warmed to rt and stirred for 30 min. After cooling the mixture to -78°C, (1R,1'R,2S,2'S)-1,1'-bicyclopentyl-2,2'-diol bismesylate (1.01 g, 3.1 mmol) in THF (20 mL) was added over 20 min. The resulting orange solution was warmed to rt and stirred overnight. The white suspension solution was hydrolyzed with saturated aqueous NH_4Cl solution. The aqueous layer was extracted with CH_2Cl_2 (2 x 20 mL). The combined organic solution was dried over anhydrous Na_2SO_4. After removal of the solvents under reduced pressure, the residue was dissolved in CH_2Cl_2 (50 mL), then treated with BH_3·THF (10 mL, 10 mmol) at rt and the mixture was stirred overnight. The reaction mixture was added to NH_4Cl aqueous solution, and extracted with CH_2Cl_2 (2 x 50 mL). The combined organic solution was dried over anhydrous Na_2SO_4. After evaporation of the solvent under reduced pressure, the residue was subjected to column chromatography on silica gel, eluting with CH_2Cl_2/hexane (1:5) and then CH_2Cl_2/hexane

(2:3) affording the product as a white solid. Yield: 0.36 g (21 %). ^{1}H-NMR ($CDCl_3$) δ 7.80-7.30 (m, 20 H, Ph), 2.55-2.35 (m, 2 H, C<u>H</u>P(BH_3)Ph_2), 1.95-1.35 (m, 14 H, CH_2 and CH), 1.7-0.5 (broad, 6 H, BH_3). ^{31}P-NMR ($CDCl_3$): δP = 17.5 (br). ^{13}C-NMR ($CDCl_3$) δ 133.43 (d, ^2J(PC) = 8.5 Hz, C_{ortho}), 132.25 (d, ^2J(PC) = 8.5 Hz, C_{ortho}), 132.08 (d, ^1J(PH) = 50.0 Hz, C_{ipso}), 130.67 (d, ^4J(PC) = 2.1 Hz, C_{para}), 130.57 (d, ^4J(PC) = 2.1 Hz, C_{para}), 129.71 (d, ^1J(PC) = 56.5 Hz, C_{ipso}), 128.39 (d, ^3J(PC) = 9.4 Hz, C_{meta}), 128.29 (d, ^3J(PC) = 9.1 Hz, C_{meta}), 46.28 (dd, J(PC) = 2.1 and 4.8 Hz, $C_{1,1'}$), 36.26 (d, ^1J(PC) = 30.6 Hz, $C_{2,2'}$), 31.19 (CH_2), 29.52 (CH_2), 22.51 (CH_2); MS m/z 520 (8.95), 506 (3.55), 429(19.10), 321(100), 253(7.45), 185(26.64), 108(43.68), 91(11.99), 77(6.88). HRMS cacld for $C_{28}H_{31}P_2$ (M^+-B_2H_6-Ph): 429.1901, found: 429.1906.

Example 4

(as depicted in Scheme 2 and Figure 8)

(2R, 2'R)-Bis(diphenylphosphino)-(1R, 1'R)-dicyclopentane (1)

To a solution of teh above borane complex of the phosphine (0.24 g, 0.45 mmol) in CH_2Cl_2 (4.5 mL) was added tetrafluoroboric acid-dimethyl ether complex (0.55 mL, 4.5 mmol) dropwise via syringe at -5 °C. After the addition, the reaction mixture was allowed to warm slowly to rt, and stirred for 20 h. The mixture was diluted with CH_2Cl_2, and neutralized with saturated aqueous $NaHCO_3$ solution. The aqueous layer was extracted with CH_2Cl_2. The combined organic solution was washed with brine, followed by water, and dried over Na_2SO_4. Evaporation of the solvent gave the pure phosphine. Yield: 0.21 g (93%). ^{1}H NMR ($CDCl_3$, 360 MHz) δ 7.52-7.27 (m, 20 H), 2.53 (m, 2 H), 2.27 (m, 2 H), 1.93(m, 2 H), 1.72(m, 2 H), 1.70-1.43 (m, 8 H); ^{13}C NMR ($CDCl_3$) δ 139-127 (Ph), 45.9 (d, J = 12.1 Hz), 45.8 (d, J = 12.0 Hz), 40.34 (d, J = 14.0 Hz), 30.9 (m), 23.8 (m); ^{31}P NMR ($CDCl_3$) δ -14.6. This phosphine was fully characterized by its borane complex.

Example 5

General Procedure for Asymmetric Hydrogenation

To a solution of $[Rh(COD)_2]BF_4$ (5.0 mg, 0.012 mmol) in THF (10 mL) in a glovebox was added chiral ligand **1** (0.15 mL of 0.1 M solution in toluene, 0.015 mmol), and Et_3N (0.087 mL, 0.62 mmol). After stirring the mixture for 30 min, the dehydroamino acid (1.2 mmol) was added. The hydrogenation was performed at rt under 1 atm of hydrogen for 24 h. The reaction mixture was treated with CH_2N_2, then concentrated in Vacuo. The residue was passed through a short silica gel column to remove the catalyst. The enantiomeric excesses were measured by GC using a Chirasil-VAL III FSOT column. The absolute configuration of products was determined by comparing the observed rotation with the reported value. All reactions went in quantitative yield with no by-products found by GC.

Example 6

(as depicted in Scheme 5 and Figure 12)

(1R, 2S, 4R, 5S)-(+)-2,5-Dimethyl-7-phenyl-7-phosphabicyclo[2.2.1]heptane borane (5)

To phenylphosphine (3.0 ml, 27.3 mmol) in THF (200 mL) was added n-BuLi (34.5 mL of a 1.6 M solution in hexane, 55 mmol) via syringe at -78°C over 20 min. Then the orange solution was warmed up to rt and stirred for 1 hr at rt. To the resulting orange-yellow suspension was added a solution of (1*S*,2*S*,4*S*,5*S*)-2,5-dimethyl-cyclohexane-1,4-diol bis(methanesulfonate) (**3**, 8.25 g, 27.5 mmol) in THF (100 mL) over 15 min. After the mixture was stirred overnight at rt, the pale-yellow suspension was hydrolyzed with saturated NH_4Cl solution. The mixture was extracted with ether (2 x 50 mL), and the combined organic solution was dried over anhydrous sodium sulfate. After filtration , the solvents were removed under reduced pressure. The residue was dissolved in methylene chloride (100 mL), treated with BH_3·THF (40 mL of a 1.0 M solution in THF, 40 mmol) and the mixture was stirred overnight. It was then pured into saturated NH_4Cl solution and extracted with CH_2Cl_2 (3 x 50 mL). The combined organic solution was dried over anhydrous Na_2SO_4 and filtered, the solvent was removed on reduced pressure. The residue was subjected to chromatography on silicon gel column, eluted with hexanes/CH_2Cl_2 (4:1) affording the product as a white solid. Yield: 1.95 g (31%). $[\alpha]^{25}_D$

= - 59.5° (c 1.07, $CHCl_3$). ^{1}H-NMR ($CDCl_3$) δ 7.60-7.30 (m, 5 H, $C_6\underline{H}_5$), 2.60-2.40 (m, 2 H, $C\underline{H}P(BH_3)Ph$), 2.15-2.05 (m, 1 H, $C\underline{H}$), 2.04-1.80 (m, 4 H, $C\underline{H}_2$), 1.65-1.50 (m, 1 H, $C\underline{H}$), 1.32 (d, $^3J(HH)$ = 6.5 Hz, 3 H, $C\underline{H}_3$), 0.59 (d, $^3J(HH)$ = 6.7 Hz, 3 H, $C\underline{H}_3$), 1.6-0.2 (br, $B\underline{H}_3$); ^{13}C-NMR ($CDCl_3$) δ 131.74 (d, $^2J(PC)$ = 7.3 Hz, C_{ortho}), 130.56 (d, $^1J(PC)$ = 43.9 Hz, C_{ipso}), 129.92 (d, $^4J(PC)$ = 2.0 Hz, C_{para}), 128.44 (d, $^3J(PC)$ = 8.6 Hz, C_{meta}), 43.07 (d, $^1J(PC)$ = 30.5 Hz, $\underline{C}HP(BH_3)Ph$), 40.85 (d, $^1J(PC)$ = 31.6 Hz, $\underline{C}HP(BH_3)Ph$), 36.27 ($\underline{C}H_2$), 36.67 (d, $^3J(PC)$ = 13.5 Hz, CH_2), 35.91 (d, $^2J(PC)$ = 3.5 Hz, $\underline{C}H$), 34.65 (d, $^2J(PC)$ = 9.8 Hz, $\underline{C}H$), 20.78 ($\underline{C}H_3$) 20.53 ($\underline{C}H_3$); ^{31}P-NMR ($CDCl_3$) δ 36.3 (d, broad, $^1J(PB)$ = 58.8 Hz); HRMS Calcd for $C_{14}H_{22}BP$: 232.1552 (M^+); found: 232.1578; $C_{14}H_{19}P$: 218.1224 (M^+-BH_3); found: 218.1233.

Example 7

(as depicted in Scheme 5 and Figure 12)

(1R, 2R, 4R, 5R)-(+)-2,5-Diisopropyl-7-phenyl-7-phosphabicyclo[2.2.1]heptane borane (6)

Using the same procedure as in the preparation of **5**. Yield: 0.33 g (50%). $[\alpha]^{25}_D$ = - 25.5° (c 1.02, $CHCl_3$). ^{1}H-NMR ($CDCl_3$) δ 7.55-7.30 (m, 5 H, $C_6\underline{H}_5$), 2.85-2.70 9 (m, 2 H $C\underline{H}P(BH_3)Ph$), 2.30-2.20 (m, 1 H, $C\underline{H}$), 2.18-2.00 (m, 1 H, $C\underline{H}$), 1.95-1.65 (m, 4 H, $C\underline{H}_2$), 1.40-1.20 (m, 2 H, $C\underline{H}$), 1.03 (d, $^3J(PH)$ = 6.5 Hz, $C\underline{H}_3$), 0.87 (d, $^3J(PH)$ = 6.7 Hz, $C\underline{H}_3$), 0.85 (d, $^3J(PH)$ = 7.4 Hz, $C\underline{H}_3$), 0.53 (s, broad, 3 H, $C\underline{H}_3$), 1.5-0.2 (broad, $B\underline{H}_3$); ^{13}C-NMR ($CDCl_3$) δ 131.19 (d, $^2J(PC)$= 8.3 Hz, C_{ortho}), 130.71 (d, $^1J(PC)$ = 45.2 Hz, C_{ipso}), 129.97 (d, $^4J(PC)$ = 2.5 Hz, C_{para}), 128.45 (d, $^3J(PC)$ = 9.5 Hz, C_{meta}), 50.30 (d, $^2J(PC)$ = 2.1 Hz, CH), 48.77 (d, $^2J(PC)$ = 9.7 Hz, CH), 38.27 (d, $^1J(PC)$ = 30.5 Hz, $\underline{C}HP(BH_3)Ph$), 36.81 (CH_2), 36.71 (d, $^1J(PC)$ = 31.5 Hz, $\underline{C}HP(BH_3)Ph$), 34.73 (d, $^3J(PC)$ = 13.7 Hz, CH_2), 31.92 ($\underline{C}HMe_2$), 31.12 ($\underline{C}HMe_2$), 22.41 (CH_3), 21.55 (CH_3), 20.73 (CH_3), 20.10 (CH_3); ^{31}P-NMR ($CDCl_3$) δ 36.d (d, broad, $^1J(PB)$ = 51.4 Hz).

Example 8

(as depicted in Scheme 5 and Figure 12)

(1R, 2S, 4R, 5S)-(+)-2,5-Dimethyl-7-phenyl-7-phosphabicyclo[2.2.1]heptane (40)

To a solution of corresponding borane complex of the phosphine (5, 1.0 g, 4.31 mmol) in CH_2Cl_2 (22 mL) was added tetrafluoroboric acid-dimethyl ether complex (2.63 mL, 21.6 mmol) dropwise via a syringe at -5 °C. After the addition, the reaction mixture was allowed to warm up slowly, and stirred at rt. After 20 h, ^{31}P NMR showed the reaction was over, it was diluted by CH_2Cl_2, neutralized by saturated $NaHCO_3$ aqueous solution. The aqueous layer was extracted with CH_2Cl_2. The combined organic solution was washed with brine, followed by water, and then dried over Na_2SO_4. Evaporation of the solvent gave a pure phosphine product, which was confirmed by NMR. Yield: 0.9 g (96%). $[\alpha]^{25}_D$ = −92.5° (c 2.3, toluene); ^1H NMR ($CDCl_3$, 360 MHz) δ 7.38-7.34 (m, 2H), 7.26-7.21 (m, 2H), 7.19-7.16 (m, 1H), 2.60-2.54 (m, 2H), 1.89-1.62 (m, 5H), 1.44-1.42 (m, 1H), 1.16 (d, J = 6.12 Hz, 3H), 0.55 (d, J = 6.95 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 138.68 (d, J = 29.3 Hz), 131.42 (d, J = 13.0 Hz), 127.88 (d, J = 2.35 Hz), 126.57 (s), 47.34 (d, J = 13.5 Hz), 45.26 (d, J = 10.2 Hz), 39.21 (d, J = 6.7 Hz), 39.21 (d, J = 5.3 Hz), 38.74 (d, J = 6.7 Hz), 34.69 (d, 17.2 Hz), 22.37 (d, J = 7.8 Hz), 21.52 (s); ^{31}P NMR($CDCl_3$) δ -7.29.

Example 9

(as depicted in Scheme 5 and Figure 12)

(1R, 2R, 4R, 5R)-(+)-2,5-Diisopropyl-7-phenyl-7-phosphabicyclo[2.2.1]heptane (8 in scheme 5)

Using the same procedure as in the preparation of 7. Yield: 1.0 g (95.5%). $[\alpha]^{25}_D$ = +43.9° (c 1.2, toluene); ^1H NMR ($CDCl_3$, 360 MHz) δ 7.35-7.30 (m, 2H), 7.24-7.14 (m, 3H), 2.94-2.85 (m, 2H), 1.76-1.53 (m, 5H), 1.25-1.14 (m, 2H), 1.06 (d, J = 7.77 Hz, 3H), 0.95-08.0 (m, 1H), 0.87 (dd, J = 3.77 Hz, 7.89 Hz, 6 H), 0.49 (d, J = 9.30 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 138.83 (d, J = 30.49 Hz), 130.69 (d, J = 12.2 Hz), 127.71 (d, J = 2.87 Hz), 126.45 (s), 53.38 (d, J = 6.34 Hz), 48.63 (d, J = 17.06 Hz), 41.97 (d, J = 13.43

Hz), 40.51 (d, J = 9.96 Hz), 37.60 (d, J = 11.09 Hz), 37.39 (d, J = 9.74 Hz), 33.03 (d, 6.11 Hz), 31.86 (s), 21.89 (s), 21.78 (s), 21.23 (s), 20.40 (s); ^{31}P NMR($CDCl_3$) δ -7.49.

Example 10

Enantioselective Allylic Alkylation

The procedures are exemplified by the experiments carried out with ligand 7 in toluene. To a stirring solution of $[Pd_2(\eta^3\text{-}C_3H_5)_2Cl_2]$ (3.0 mg, 0.008 mmol) in toluene (1.5 mL) was added ligand 7 (0.36 mL of 0.1 M solution in toluene, 0.036 mmol) under a nitrogen atmosphere. After 30 mins, racemic 1,3-diphenyl-1-acetoxypropene (150 mg, 0.60 mmol) was added. Then the solution was allowed to be stirred 30 mins. N,O-bis(trimethylsiyl)acetamide (0.44 mL, 1.8 mmol), dimethyl malonate (0.21 mL, 1.8 mmol) and potassium acetate (3 mg, 0.03 mmol) were added in this order. The reaction was monitored by TLC (eluent: Hexane / ethyl acetate = 10/1). After 1.5 hrs, TLC showed the reaction was over. After the solvent was evaporated in vacuo, column chromatography on silica gel (eluent: Hexane / ethyl acetate = 10/1) of the residue yielded the pure product : Yield: 190 mg, 97.7% . The optical purity was determined to be 95.5% ee by HPLC (Daicel Chiralcel OD column, 1 ml/min, hexane /2-propanol = 99/1).

Example 11

Typical Procedure for Hydrogenation of Imines

To a solution of chloro(1,5cyclooctadiene)iridium(I) dimer (2 mg, 0.003 mmol) in toluene (4 mL) was added a solution of BICP in toluene (0.1 M, 71 ul, 0.0071mmol), the resulting solution was stirred in glovebox for 30 min. Then phthalimide (3.5 mg, mmol) was added and the reaction mixture was stirred for another 30 min before 2,3,3-trimethylindolenine (96 ul, 0.6 mmol) was added. The reaction tube was placed in an autoclave, pressurized with hydrogen to 1000psi after several exchange with hydrogen, and stirred at rt for 65 h. Conversion (97.8%) and enantiomeric excess (92.2%) were determined by GC (a capillary column: γ-dex-225).

Example 12

(as depicted in Scheme 3, Figure 5 and Figure 11)

Me-PennPhos: 1,2-Bis{(1R,2S,4R,5S)-2,5-dimethyl-8-phenylphospha-bicyclo[2.2.1]heptyl}benzene (36a)

To the suspension of NaH (8.0 g, 333 mmol) in THF (200 ml), cooled to 0°C, was added 1,2-diphosphinobenzene (4.0 ml, 30.4 mmol), followed by HMPA (80 ml). The resulting orange suspension was stirred at 0°C for 1 h. (1S,2S,4S,5S)-2,5-dimethylcyclohexane-1,4-diol dimesolate (18.3 g, 60.9 mmol) in THF (150 ml) was added over 20 min. The resulting orange-red suspension was stirred at RT for 3.5 days, hydrolyzed with NaCl-H_2O and then extracted with hexane (2 x 100 ml). The combined organic solution was dried over Na_2SO_4. After filtration, the solvents were removed under reduced pressure. The residue was subjected to chromatography on silica gel column, eluted with hexane. Yield: 3.0 g (27.5%). ^{1}H-NMR ($CDCl_3$): δH = 7.25-7.10 (m, 2 H, aromatic), 7.08-6.95 (m, 2 H, aromatic), 3.21 (d, broad, 2 H, ^2J(PH) = 14.5 Hz, PCH), 2.58 (d, broad, 2 H, ^2J(PH) = 13.4 Hz, PCH), 1.90-1.60 (m, 12 H), 1.55-1.35 (m, 2 H,), 1.17 (d, 6 H, ^3J(HH) = 6.3 Hz, CH_3), 0.60 (d, 6 H, ^3J(HH) = 6.3 Hz, CH_3). CH. ^{13}C-NMR (is out of first order, $CDCl_3$): δC = 143.94, 143.66, 143.48, 143.20, 131.05, 131.00, 130.93, 126.33, 46,24, 46.20, 46,17, 46.13, 45.92, 45.69, 45.61, 45.38, 40.17, 40.05, 39.89, 39.73, 39.61, 39.52, 39.33, 39.29, 39.26, 34.76, 34.61, 34.51, 34.41, 34.26, 22.69, 22.65, 22.61, 20.82. ^{31}P-NMR ($CDCl_3$): δP = -7.3 ppm.

Example 13

(as depicted in Scheme 3 and Figure 11)

i-Pr-PennPhos: 1,2-Bis{(1R,2R,4R,5R)-2,5-bis-isopropyl-8-phenylphos-phabicyclo[2.2.1]heptyl}benzene (36b)

1,2-diphosphinobenzene (0.4 ml, 3.04 mmol) and NaH (0.9 g, 37.5 mmol) were mixed in THF (50 ml) and cooled to 0°C. HMPA (8.5 ml, 49 mmol) was added. The resulting orange suspension was stirred at 0°C for 1 h and then (1S,2S,4S,5S)-2,5-dimethyl-cyclohexane-1,4-diol dimesolate (2.17 g, 6.08 mmol) in THF (40 ml) was added over 10 min. The resulting orange-red suspension was stirred at RT for 3 days. After cooled to 0°C, it was hydrolyzed with NaCl-H_2O, and extracted with hexane (2 x 50 ml).

The combined organic solution was dried over Na_2SO_4 and filtered. The solvents were removed under reduced pressure. The residue was subjected to chromatography on silica gel column, eluted with hexane. Yield: 0.6 g (42%). ^{1}H-NMR ($CDCl_3$): δH = 7.20-7.10 (m, 2 H, aromatic), 7.05-6.90 (m, 2 H, aromatic), 3.38 (d, broad, 2 H, $^2J(PH)$ = 14.2 Hz, PCH), 2.85 (d, broad, 2 H, $^2J(PH)$ = 13.5 Hz, PCH), 1.85-1.45 (m, 12 H), 1.30-1.08 (m, 4 H), 1.03 (d, 6H, $^3J(HH)$ = 6.4 Hz, CH_3), 0.96 (d, 6H, $^3J(HH)$ = 5.6 Hz, CH_3), 0.86 (d, 6H, $^3J(HH)$ = 6.5 Hz, CH_3), 0.47 (s, 6 H, CH_3). ^{13}C-NMR (is out of first order, $CDCl_3$): δC = 143.97, 143.62, 143.56, 143.50, 143.45, 143.09, 130.96, 130.90, 130.86, 126.11, 54.10, 54.06, 54.03, 48.65, 48.56, 48.46, 42.02, 41.96, 41.24, 41.20, 41.18, 41.14, 37.94, 37.77, 37.60, 37.46, 33.29, 33.27, 33.24, 31.69, 23,45, 23.40, 23.35, 22.22, 20.97, 20.54. ^{31}P-NMR ($CDCl_3$): δP = -8.7 ppm.

Example 14

(as depicted in Scheme 4, Figure 4 and Figure 10)

C5-Tricyclophos: 1,2-Bis{(2R,6R,7R,11R)phosphatricyclo[3.3.0.0]undecanyl}-benzene (26)

1,2-diphosphinobenzene (0.20 ml, 1.52 mmol) and NaH (0.40 g, 16.7 mmol) were mixed in THF (50 ml) and cooled to 0°C. HMPA (4.3 ml, 25 mmol) was added. The resulting orange suspension was stirred at 0°C for 1 h and then treated with (1R,1'R,2S,2'S)-1,1'-bicyclopentyl-2,2'-diol bismesylate (0.993 g, 3.04 mmol) in THF (40 ml). The resulting orange-red suspension was stirred at RT for 20 h, pale orange-yellow suspension formed. After cooled to 0°C, it was hydrolyzed with NaCl-H_2O, and extracted with hexane (2 x 50 ml). The combined organic solution was dried over Na_2SO_4 and filtered. The solvents were removed under reduced pressure. The residue was subjected to chromatography on silica gel column, eluted with hexane/ether (40:1.5). Yield: 0.42 g (67%). ^{1}H-NMR ($CDCl_3$): δH = 7.50-7.30 (m, 2 H, aromatic), 7.25-7.10 (m, 2 H, aromatic), 3.15-2.95 (m, 2 H, PCH), 2.85-2.70 (m, 2 H, PCH), 2.50-2.30 (m, 4 H, CH), 2.05-1.00 (m, 24 H, CH_2). ^{13}C-NMR (is out of first order, $CDCl_3$): δC = . 144.03, 143.98, 130.16, 130.12, 130.08, 127.50, 53.64, 52.97, 44.72, 44.66, 44.60, 43.07, 32.64, 32.01, 31.86, 31.68, 30.58, 26.47, 25.41, 25.36, 25.31. ^{31}P-NMR ($CDCl_3$): δP = 9.6 ppm.

Example 15

General Procedure for Asymmetric Hydrogenation of Dehydroaminoacids for Pennphos ligands

In a glovebox, a schlenk reaction bottle was charged with a given amount of Rh catalyst precursor and Me-PennPhos in a ratio of 1.1 mol ligand per 1 mol Rh and 10 ml of the given solvent (dried and degassed), the resulting orange-yellow solution was stirred at rt for 20 min. Then substrate (1 mmol, sub/cat = 100) was added. The nitrogen atmosphere was exchanged to H_2 by flashing the schlenk with H_2. The reaction mixture was then stirred at RT and 1 atm H_2 for a certain period of time. The reaction solution was passed through a short silica gel, washed with ether. The conversion and ee were measured by GC analysis on Chirasil-Val III column. The absolute configuration was determined by measuring the rotation of product and comparing with the corresponding standard values.

Example 16

General Procedure for Asymmetric Hydrogenation of Ketones

In a glovebox, a reaction bottle was charged with $[Rh(COD)Cl]_2$ (2.5 mg, 0.0101 mmol) and Me-PennPhos (3.7 mg, 0.0103 mmol), and MeOH (10 ml, dried and degassed), the resulting orange-yellow solution was stirred at rt for 30 min. Then ketone substrate (1 mmol, substrate /catalyst = 100) was added. The reaction solution was then placed in an autoclave. The nitrogen atmosphere was exchanged to H_2 by flashing the autoclave with H_2 (10 to 20 atm). The autoclave was pressurized to a certain atmosphere of H_2. The reaction mixture was then stirred at RT for a given period of time. The reaction solution was then passed through a short silica gel, washed with ether. The conversion and ee were measured by GC analysis on chiral β–dex 120 column. The absolute configuration was determined by measuring the rotation of product and comparing with the corresponding standard values.

Example 17

General Procedure for Asymmetric Hydrogenation of beta-Keto esters

BICP (0.01 mol) and Ru(COD)(2-methylallyl)$_2$ (0.01 mol) were placed in a 10 ml Schlenk tube and the vessel was purged with argon. 2 mL of anhydrous acetone were added. To this suspension was added methanolic HBr (0.11 ml of a 0.29 M solution) and the suspension was stirred 30 min at rt. The solvent was thoroughly evaporated under vacuum and the Ru(BICP)Br$_2$ obtained was used immediately. The solution of appropriate substrate (1 mmol) in degassed solvent (2 ml) was placed in a 10 ml Schlenck tube and degasses by 3 cycles of vacuum/ argon. This mixture was added to the catalyst (1%) in a glass vessel and placed under argon in 300 ml stainless steel autoclave. The Argon atmosphere was replaced with hydrogen. The hydrogenations were run under the reaction conditions given The solvent was removed under pressure. Conversion and ee are determined by chiral GC column β-dex 120 and γ-dex 225.

The above examples illustrate the present invention and are not intended to limit the invention in spirit or scope.

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CLAIMS

What is claimed is:

1. A chiral phosphine ligand comprising a conformationally rigid cyclic structure, wherein the phosphorus is bonded to or is part of the cyclic structure, whereby the ligand rigidity provides enhanced chiral discrimination in metal catalyzed asymmetric organic reactions, and wherein the phosphine ligand is selected from the group consisting of a chiral phosphine ligand comprising:

   i) a) a 2,2'-bis(diorganophosphino)-1,1'-bis(cyclic) structure wherein each cycle of the bis(cyclic) structure comprises 3 to 8 carbon atoms wherein the 1, 1', 2 and 2' carbon atoms in the bis(cyclic) structure are saturated carbon atoms and wherein the carbon atoms in the bis(cyclic) structure other than the 1, 1', 2 and 2' carbon atoms are optionally replaced with nitrogen;

   b) a 1,1'-bis(cyclic)-2,2'(organophosphinite) structure;

   c) a chiral phosphine ligand comprising a heteroatom-containing spiro bis-organophosphine or organophosphinite;

   d) a chiral bidentate phosphine ligand comprising a (bis)phospha-tricyclic structure with a bridge group;

   e) a chiral phosphine ligand comprising a (bis)fused phospha-bicyclic structure comprising a bridge structure;

   f) a chiral phosphine ligand comprising a cis(bis) phosphine fused bicyclic structure;

   g) a chiral phosphine ligand comprising a trans(bis) phosphine bicyclic structure;

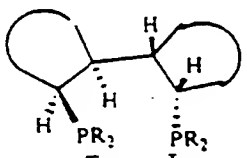
   h) a chiral phosphine ligand comprising a cis or trans biphosphine cyclic structure having two R' substituents selected from the group consisting of alkyl, fluoroalkyl or perfluoroalkyl, each having up to 8 carbon atoms, aryl, substituted aryl, arylalkyl, ring-substituted arylalkyl, and $-CR'_2(CR'_2)_qZ(CR'_2)_pR'$ wherein q and p are the same or different integers ranging from 1 to 8; Z is defined as O, S, NR, PR, AsR, SbR, divalent aryl, divalent fused aryl, divalent 5-membered ring heterocyclic

group, or a divalent fused heterocyclic group where R is selected from the group consisting of alkyl of 1-8 carbon atoms, aryl, and substituted aryl; or

ii) a chiral monodentate phosphine ligand comprising a phospha-tricyclic structure.

2. A cyclic phosphine ligand of claim 1 having a structure selected from the group consisting of :

A. Bidentate cyclic chiral phosphines:



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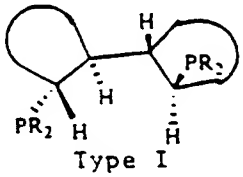

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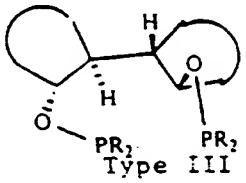

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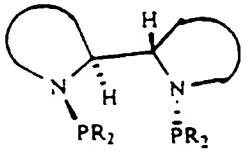

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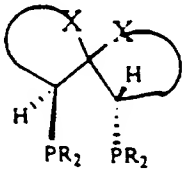

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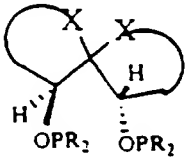

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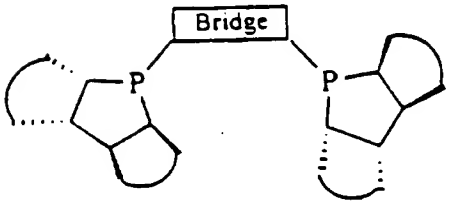

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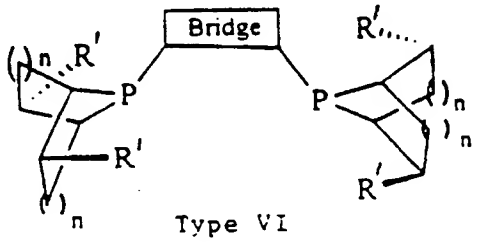

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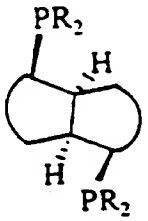

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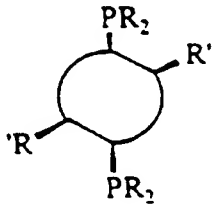

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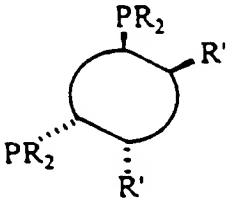

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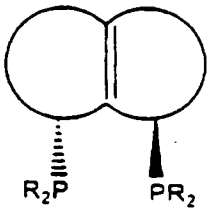
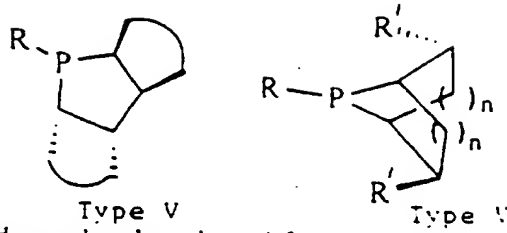


Type VIIc

or

B. monodentate cyclic chiral phosphines



Type V Type VI

wherein each R is independently selected from the group consisting of alkyl of 1-8 carbon atoms, aryl, and substituted aryl;

each R' is independently selected from the group consisting of alkyl, fluoroalkyl and perfluoroalkyl, each having up to 8 carbon atoms; aryl; substituted aryl; arylalkyl; ring-substituted arylalkyl; and $-CR'_2(CR'_2)_qZ(CR'_2)_pR'$ wherein q and p are the same or different integers ranging from 1 to 8, R' is as defined above, and Z is selected from the group consisting of O, S, NR, PR, AsR, SbR, divalent aryl, divalent fused aryl, divalent 5-membered ring heterocyclic group, and a divalent fused heterocyclic group where R is as defined above;

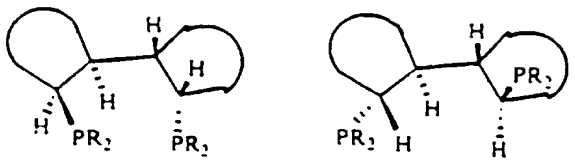
the cyclic structure D represents a ring having 3 to 8 carbon atoms and the cyclic structure ⊃ represents a ring having 0 to 8 carbon atoms; each of which may be substituted within the ring with one or more oxygen, sulfur, N-R', C=O, or CR'_2, wherein the ring may further be substituted with R' as defined above;

the Bridge is selected from the group consisting of $-(CH_2)_r-$ where r is an integer ranging from 1 to 8; $-(CH_2)_sZ(CH_2)_m-$ wherein s and m are each the same or different integers ranging from 1 to 8; 1,2-divalent phenyl; 2,2'divalent-1,1'biphenyl; 2,2'divalent 1,2'binapthyl; and ferrocene; each of which may be substituted with R' as defined above; and wherein the substitution on 1,2-divalent phenyl, the ferrocene or biaryl bridge is independently selected from the group consisting of hydrogen, halogen, alkyl, alkoxyl, aryl, aryloxy, nitro, amino, vinyl, substituted vinyl, alkynyl, or sulfonic acids;

X is selected from the group consisting of O, S and NR where R is as defined above; and,

n is 1 or 2.

3. A cyclic chiral phosphine ligand, according to claim 1, having the following structure:

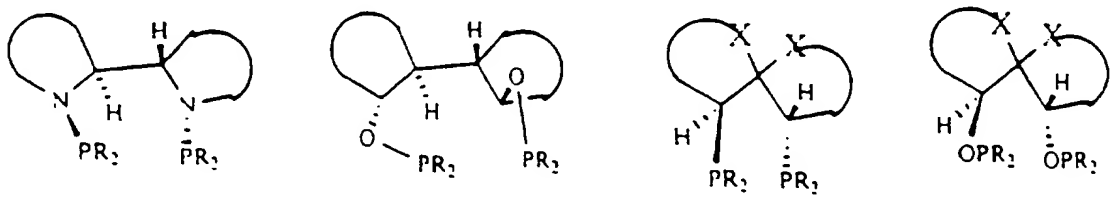


wherein each R is independently selected from the group consisting of aryl, substituted aryl, or alkyl of 1-8 carbon atoms;

the cyclic structure D represents a ring having 3 to 8 carbon atoms which may be substituted within the ring with one or more oxygen, sulfur, N-R', C=O, or CR'_2, wherein the ring may further be substituted with R' wherein R' is selected from the group consisting of alkyl, fluoroalkyl and perfluoroalkyl, each having up to 8 carbon atoms; aryl; substituted aryl; arylalkyl; ring-substituted arylalkyl; and $-CR'_2(CR'_2)_qZ(CR'_2)_pR'$ wherein q and p are the same or different integers ranging from 1 to 8, R' is as defined above, and Z is selected from the group consisting of O, S, NR, PR, AsR, SbR, divalent aryl, divalent fused aryl, divalent 5-membered ring heterocyclic group, and a divalent fused heterocyclic group where R is as defined above.

4. A cyclic chiral phosphine ligand, according to claim 3, selected from the group consisting of structures 1-13 as illustrated in Figure 2.

5. A cyclic phosphine ligand, according to claim 1, having the following structure:



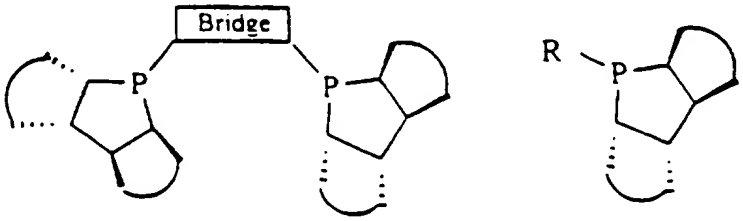
wherein each R is independently selected from the group consisting of aryl, substituted aryl, or alkyl of 1-8 carbon atoms;

the cyclic structure D represents a ring having 3 to 8 carbon atoms which may be substituted within the ring with one or more oxygen, sulfur, N-R', C=O, or CR'_2, wherein the ring may further be substituted with R' wherein R' is selected from the group consisting of alkyl, fluoroalkyl and perfluoroalkyl, each having up to 8 carbon atoms; aryl; substituted aryl; arylalkyl; ring-substituted arylalkyl; and $-CR'_2(CR'_2)_qZ(CR'_2)_pR'$ wherein q and p are the same or different integers ranging from 1 to 8, R' is as defined above, and Z is selected from the group consisting of O, S, NR, PR, AsR, SbR, divalent aryl, divalent fused aryl, divalent 5-membered ring heterocyclic group, and a divalent fused heterocyclic group where R is as defined above; and,

X is selected from the group consisting of O, S and NR where R is as defined above.

6. A cyclic chiral phosphine ligand, according to claim 5, which is selected from the group consisting of structures 14-23 as illustrated in Figure 3.

7. A cyclic phosphine ligand, according to claim 1, having the following structure:



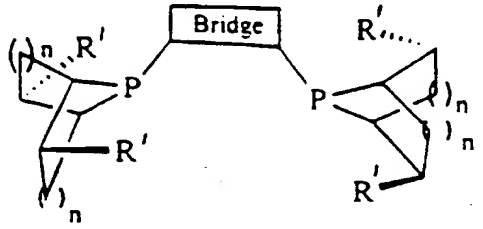
wherein each R is independently selected from the group consisting of aryl, substituted aryl, or alkyl of 1-8 carbon atoms;

the cyclic structure D represents a ring having 3 to 8 carbon atoms which may be substituted within the ring with one or more oxygen, sulfur, N-R', C=O, or CR'_2, wherein the ring may further be substituted with R' wherein R' is selected from the group consisting of alkyl, fluoroalkyl and perfluoroalkyl, each having up to 8 carbon atoms; aryl; substituted aryl; arylalkyl; ring-substituted arylalkyl; and $-CR'_2(CR'_2)_qZ(CR'_2)_pR'$ wherein q and p are the same or different integers ranging from 1 to 8, R' is as defined above, and Z is selected from the group consisting of O, S, NR, PR, AsR, SbR, divalent aryl, divalent fused aryl, divalent 5-membered ring heterocyclic group, and a divalent fused heterocyclic group where R is as defined above; and,

the Bridge is selected from the group consisting of $-(CH_2)_r-$ where r is an integer ranging from 1 to 8; $-(CH_2)_sZ(CH_2)_m-$ wherein s and m are each the same or different integers ranging from 1 to 8; 1,2-divalent phenyl; 2,2'divalent-1,1'biphenyl; 2,2'divalent 1,2'binapthyl; and ferrocene; each of which may be substituted with R' as defined above; and wherein the substitution on 1,2-divalent phenyl, the ferrocene or biaryl bridge is independently selected from the group consisting of hydrogen, halogen, alkyl, alkoxyl, aryl, aryloxy, nitro, amino, vinyl, substituted vinyl, alkynyl, or sulfonic acids.

8. A cyclic chiral phosphine ligand, according to claim 7, which is selected from the group consisting of structures 24-34 as illustrated in Figure 4.

9. A cyclic phosphine ligand, according to claim 1, having the following structure:



wherein each R' is independently selected from the group consisting of alkyl, fluoroalkyl and perfluoroalkyl, each having up to 8 carbon atoms; aryl; substituted aryl; arylalkyl; ring-substituted arylalkyl; and $-CR'_2(CR'_2)_qZ(CR'_2)_pR'$ wherein q and p are the same or

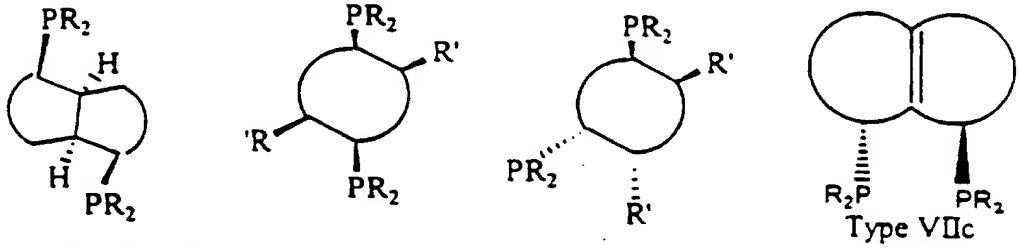
different integers ranging from 1 to 8, R' is as defined above, and Z is selected from the group consisting of O, S, NR, PR, AsR, SbR, divalent aryl, divalent fused aryl, divalent 5-membered ring heterocyclic group, and a divalent fused heterocyclic group where R is as defined above;

the Bridge is selected from the group consisting of $-(CH_2)_r-$ where r is an integer ranging from 1 to 8; $-(CH_2)_sZ(CH_2)_m-$ wherein s and m are each the same or different integers ranging from 1 to 8; 1,2-divalent phenyl; 2,2'divalent-1,1'biphenyl; 2,2'divalent 1,2'binapthyl; and ferrocene; each of which may be substituted with R' as defined above; and wherein the substitution on 1,2-divalent phenyl, the ferrocene or biaryl bridge is independently selected from the group consisting of hydrogen, halogen, alkyl, alkoxyl, aryl, aryloxy, nitro, amino, vinyl, substituted vinyl, alkynyl, or sulfonic acids; and,

n is 1 or 2.

10. A cyclic chiral phosphine ligand, according to claim 9, which is selected from the group consisting of structures 35-39 of Figure 5.

11. A cyclic phosphine ligand, according to claim 1, having the following structure:



Type VIIc

wherein each R is independently selected from the group consisting of aryl, substituted aryl, or alkyl of 1-8 carbon atoms;

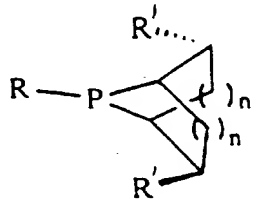
each R' is independently selected from the group consisting of alkyl, fluoroalkyl and perfluoroalkyl, each having up to 8 carbon atoms; aryl; substituted aryl; arylalkyl; ring-substituted arylalkyl; and $-CR'_2(CR'_2)_qZ(CR'_2)_pR'$ wherein q and p are the same or different integers ranging from 1 to 8, R' is as defined above, and Z is selected from the

group consisting of O, S, NR, PR, AsR, SbR, divalent aryl, divalent fused aryl, divalent 5-membered ring heterocyclic group, and a divalent fused heterocyclic group where R is as defined above; and,

the cyclic structure D represents a ring having 3 to 8 carbon atoms and the cyclic structure D represents a ring having 0 to 8 carbon atoms; each of which may be substituted within the ring with one or more oxygen, sulfur, N-R', C=O, or CR'$_2$, wherein the ring may further be substituted with R' as defined above.

12. A cyclic chiral phosphine ligand, according to claim 11, which is selected from the group consisting of structures 45-49 of Figure 7.

13. A cyclic phosphine ligand, according to claim 1, having the following structure:



wherein R is independently selected from the group consisting of aryl, substituted aryl, or alkyl of 1-8 carbon atoms;

each R' is independently selected from the group consisting of alkyl, fluoroalkyl and perfluoroalkyl, each having up to 8 carbon atoms; aryl; substituted aryl: arylalkyl; ring-substituted arylalkyl; and -CR'$_2$(CR'$_2$)$_q$Z(CR'$_2$)$_p$R' wherein q and p are the same or different integers ranging from 1 to 8, R' is as defined above, and Z is selected from the group consisting of O, S, NR, PR, AsR, SbR, divalent aryl, divalent fused aryl, divalent 5-membered ring heterocyclic group, and a divalent fused heterocyclic group where R is as defined above;and,

n is 1 or 2.

14. A cyclic chiral phosphine ligand, according to claim 13, which is selected from the group consisting of structures 40-44 as illustrated Figure 6.

15. A catalyst comprising a ligand of claim 1 complexed with a transition metal.

16. The catalyst of claim 15 wherein the transition metal is selected from the group consisting of rhodium, iridium, ruthenium, palladium and platinium.

17. In a method for transition metal complex catalyzed asymmetric hydrogenation of ketones, imines, or olefin, the improvement comprising catalysing the reaction with the catalyst of claim 16.

18. In a method for a transition metal catalyzed asymmetric reaction selected from the group consisting of hydrogenation, hydride transfer reaction, hydrosilylation, hydroboration, hydrovinylation, hydroformylation, hydrocarboxylation, allylic alkylation, cyclopropanation, Diels-Alder reaction, Aldol reaction, Heck reaction, Michael addition, and stereo-selective polymerization, the improvement comprising catalysing the reaction with a catalyst of claim 16.

19. A method of claim 18 wherein said catalyst is selected from the group consisting of compound 1 as illustrated in Figure 1, compound 36 as illustrated in Figure 5, compound 40 as illustrated in Figure 6, and compound 26 as illustrated in Figure 4.

20. A method of claim 18 wherein the catalyst is a complex of a chiral phosphine complexed with a compound selected from the group consisting of $[Rh(COD)Cl]_2$, $[Rh(COD)_2]X$; $[Ir(COD)Cl]_2$; $[Ir(COD)_2]X$, $Ru(COD)Cl_2$, $[Pd(CH_3CN)_4[BF_4]_2$, $Pd_2(dba)_3$, and $[Pd(C_3H_5)Cl]_2$; wherein X is selected from the group consisting of BF_4, ClO_4, SbF_6, and CF_3SO_3.

21. A method of claim 18 wherein the catalyst is a compound selected from the group consisting of $Ru(RCOO)_2(Y)$, $RuX_2(Y)$, $Ru(methylallyl)_2(Y)$, $Ru(aryl\ group)X_2(Y)$, wherein X is selected from the group consisting of Cl , Br and I; and, Y is a chiral diphosphine of claim 1.

22. In a method for asymmetric hydration of a ketone, imine or olefin catalyzed by a complex comprising Ru, Rh and Ir and a chiral ligand, the improvement comprising conducting the catalysis with a palladium complex having a chiral phosphine ligand of claim 1.

23. A method of claim 22 wherein said catalyst is selected from the group consisting of compound 1 as illustrated in Figure 1, compound 36 as illustrated in Figure 5, and compound 26 as illustrated in Figure 4.

24. In a method for asymmetric allyllic alkylation catalyzed by a complex comprising palladium and a chiral ligand, the improvement comprising conducting the catalysis with a palladium complex having the chiral ligand of claim 1.

25. A method of claim 24 wherein said catalyst is compound 40 as illustrated in Figure 6.

26. The chiral phosphine ligand shown as compound 1 in Figure 1.

27. The chiral phosphine ligand shown as compound 36 in Figure 5.

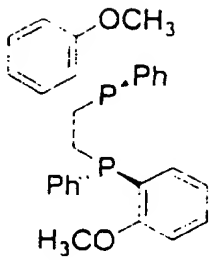
28. The chiral phosphine ligand shown as compound 40 in Figure 6.

29. The chiral phosphine ligand shown as compound 26 in Figure 4.

30. The intermediate shown as compound 3 in Scheme 2.

1/16

FIGURE 1



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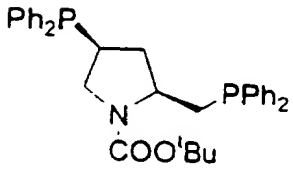

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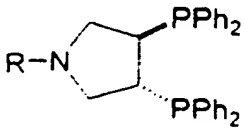

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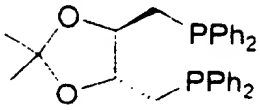
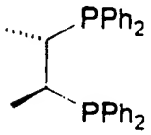
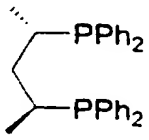


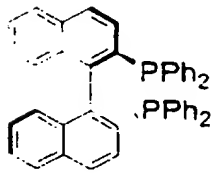
DIOP



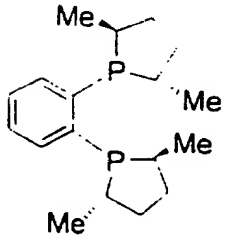
Chiraphos



Skewphos



BINAP



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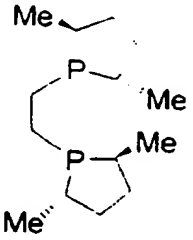

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FIGURE 2

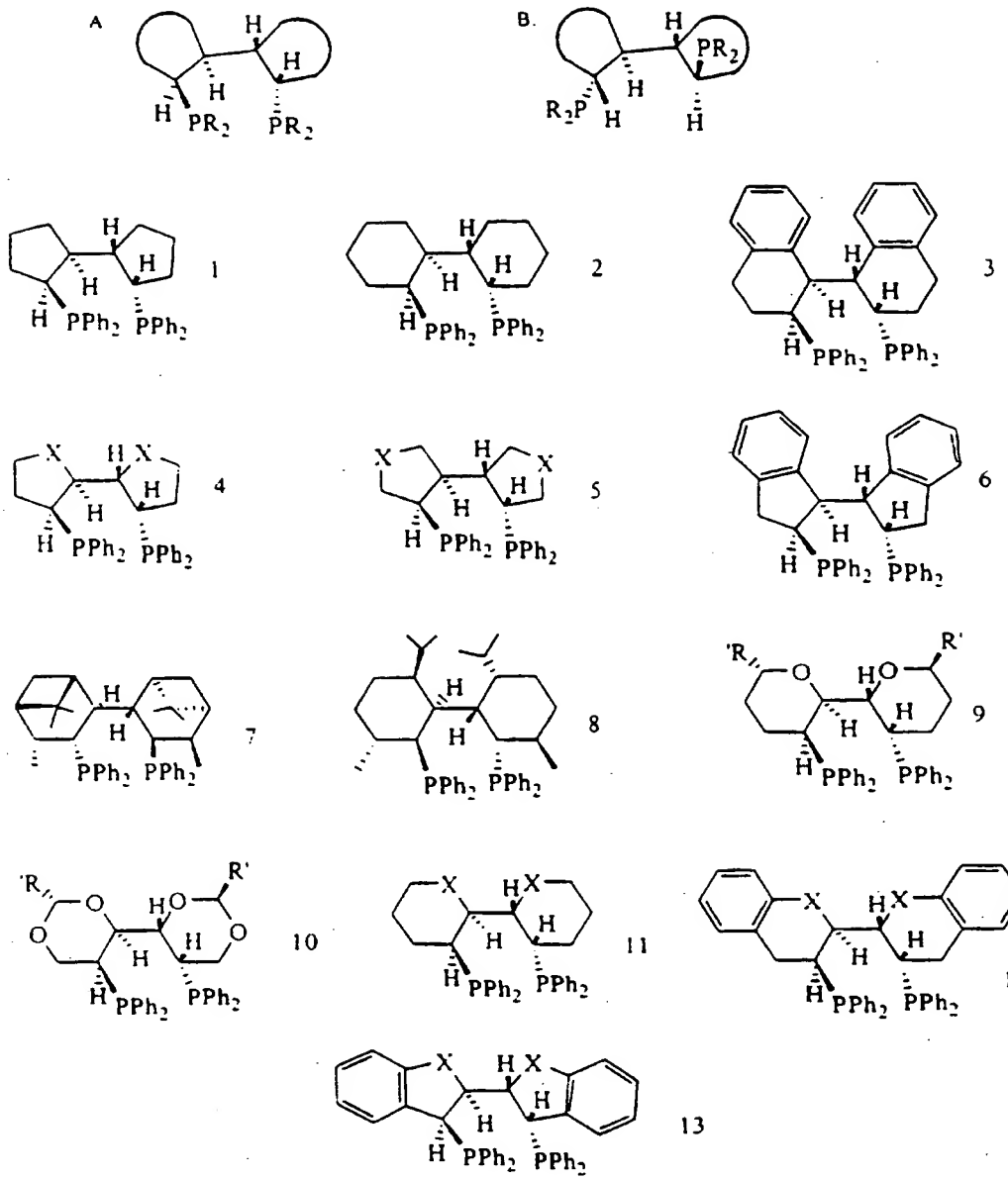
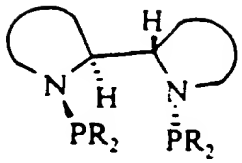
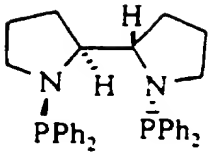


FIGURE 3

A.





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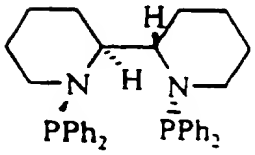

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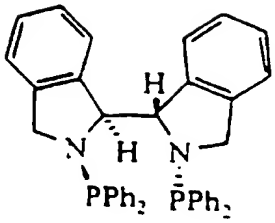

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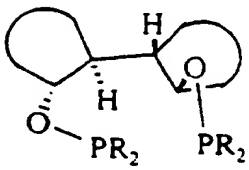
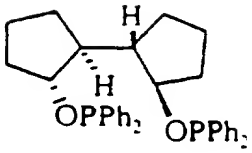
B.





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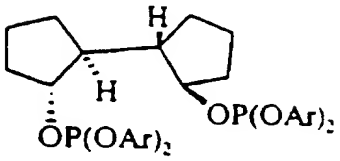

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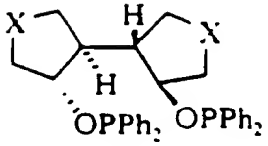

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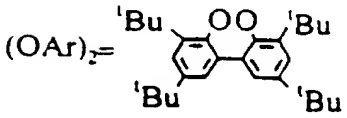
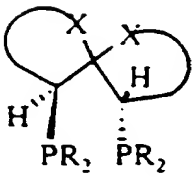
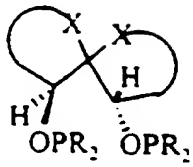
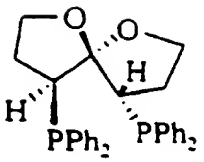


C.



D.





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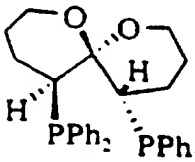

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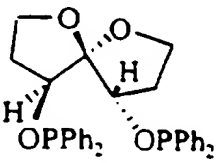

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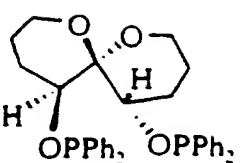

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FIGURE 4

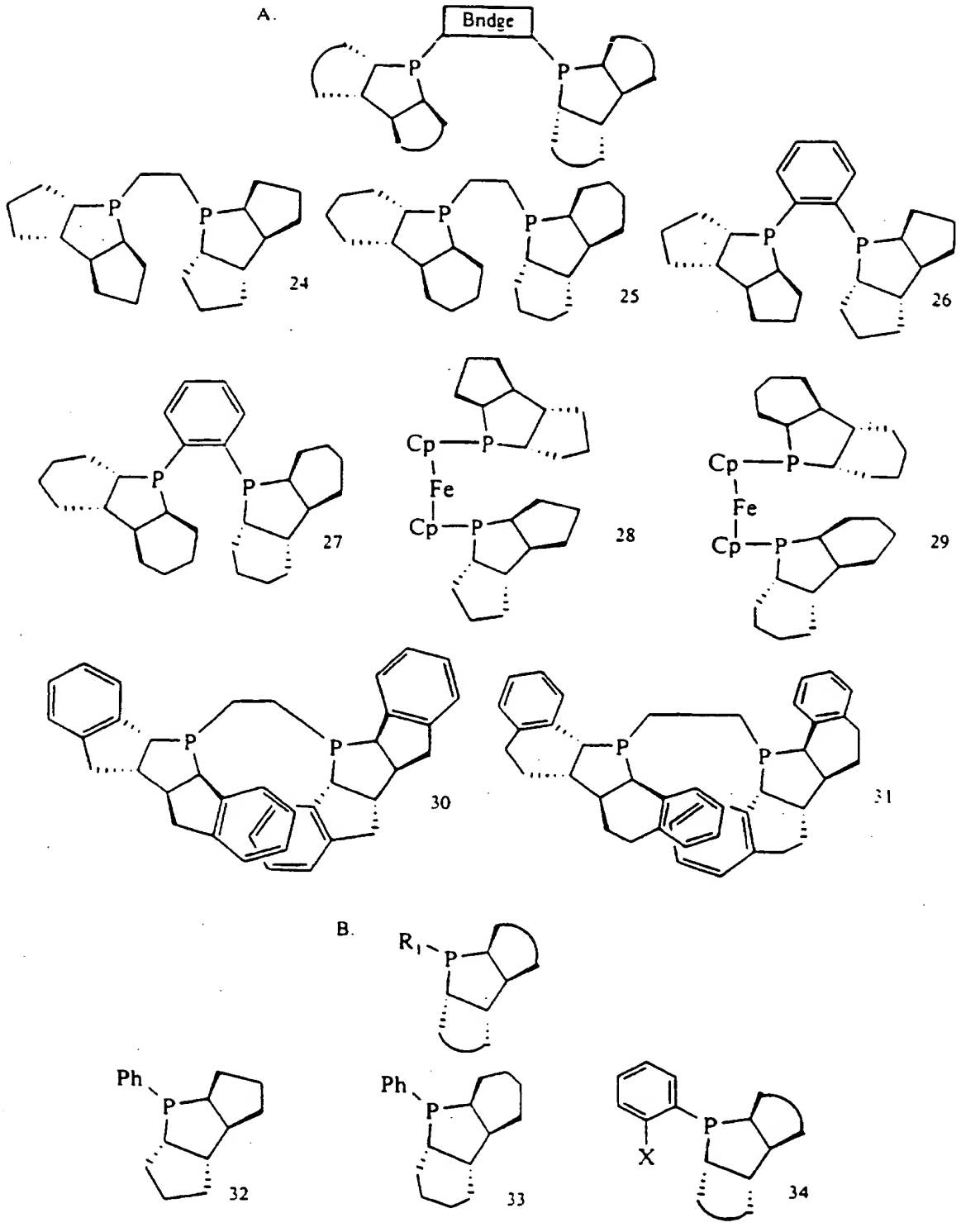

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FIGURE 5

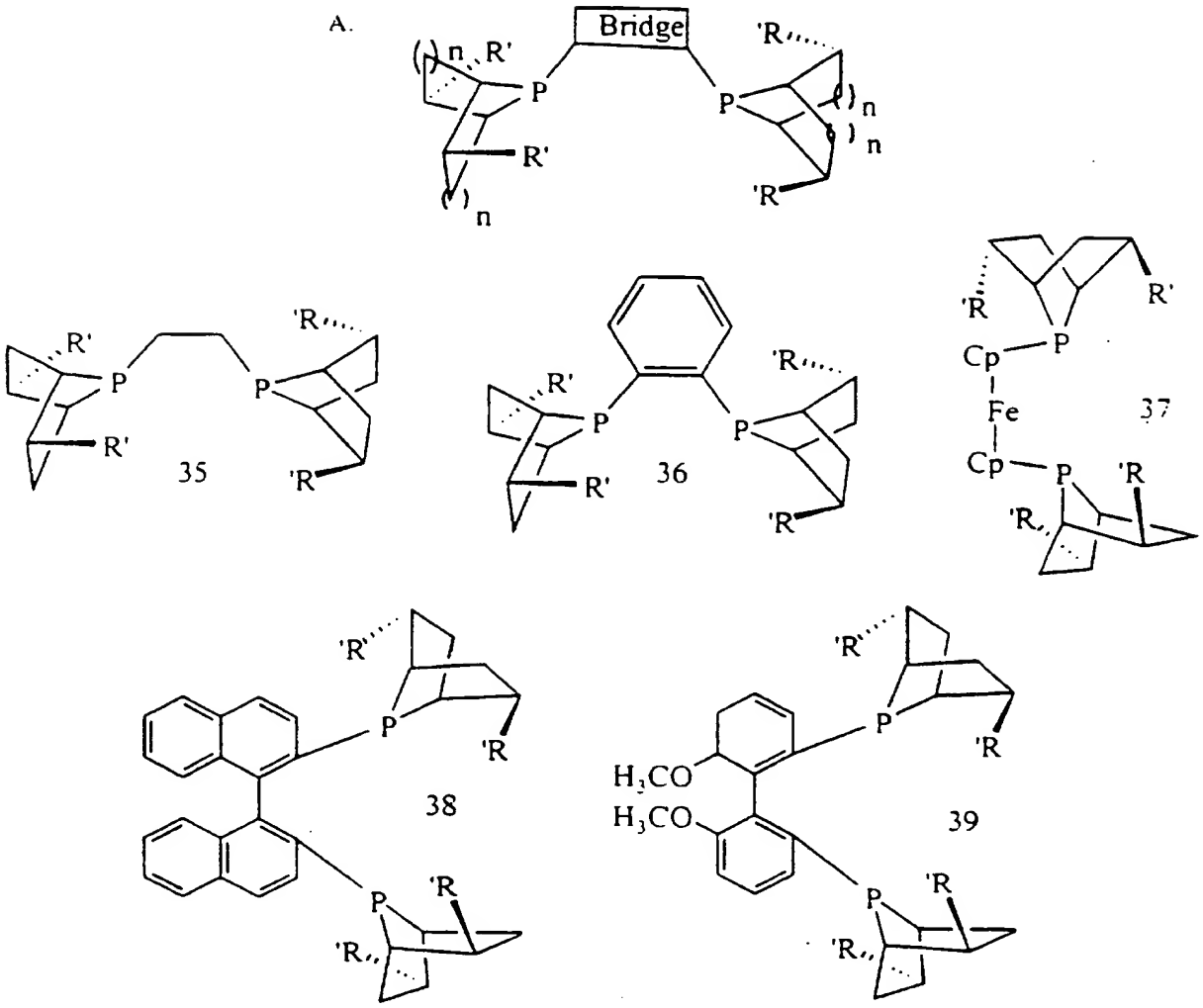
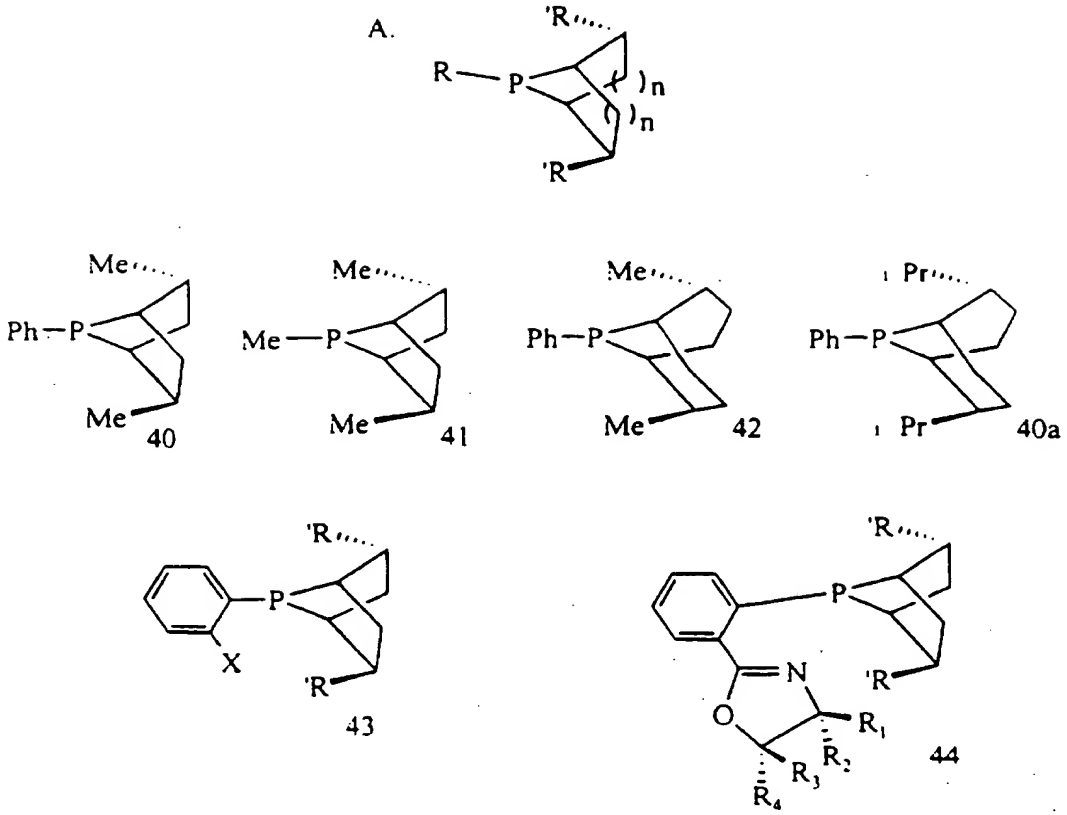


FIGURE 6


A.
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'R
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P
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O
'R
R1
R2
R3
R4
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FIGURE 7

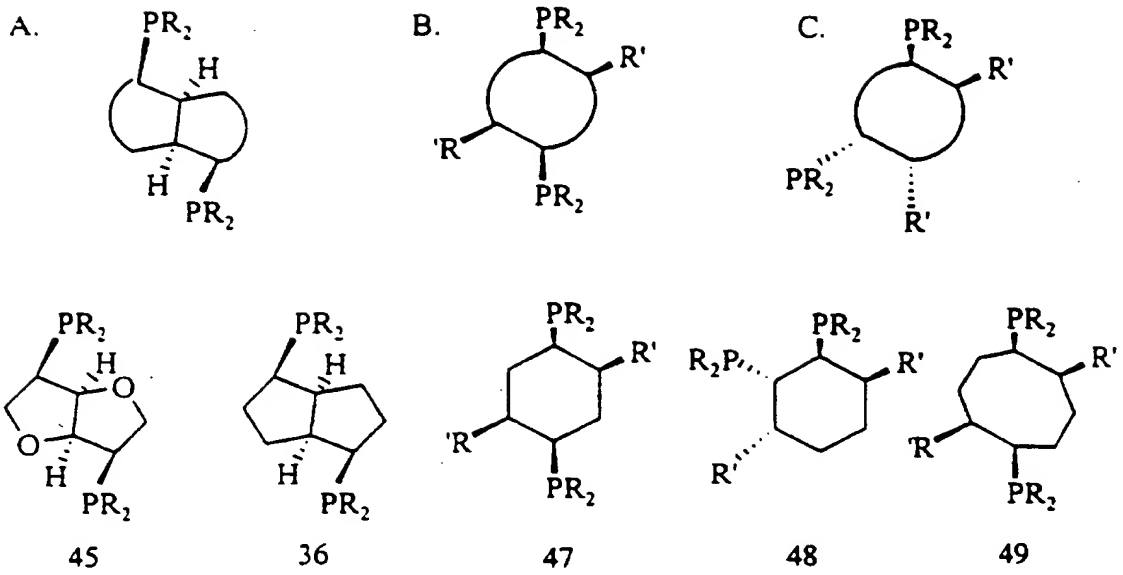

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FIGURE 8A

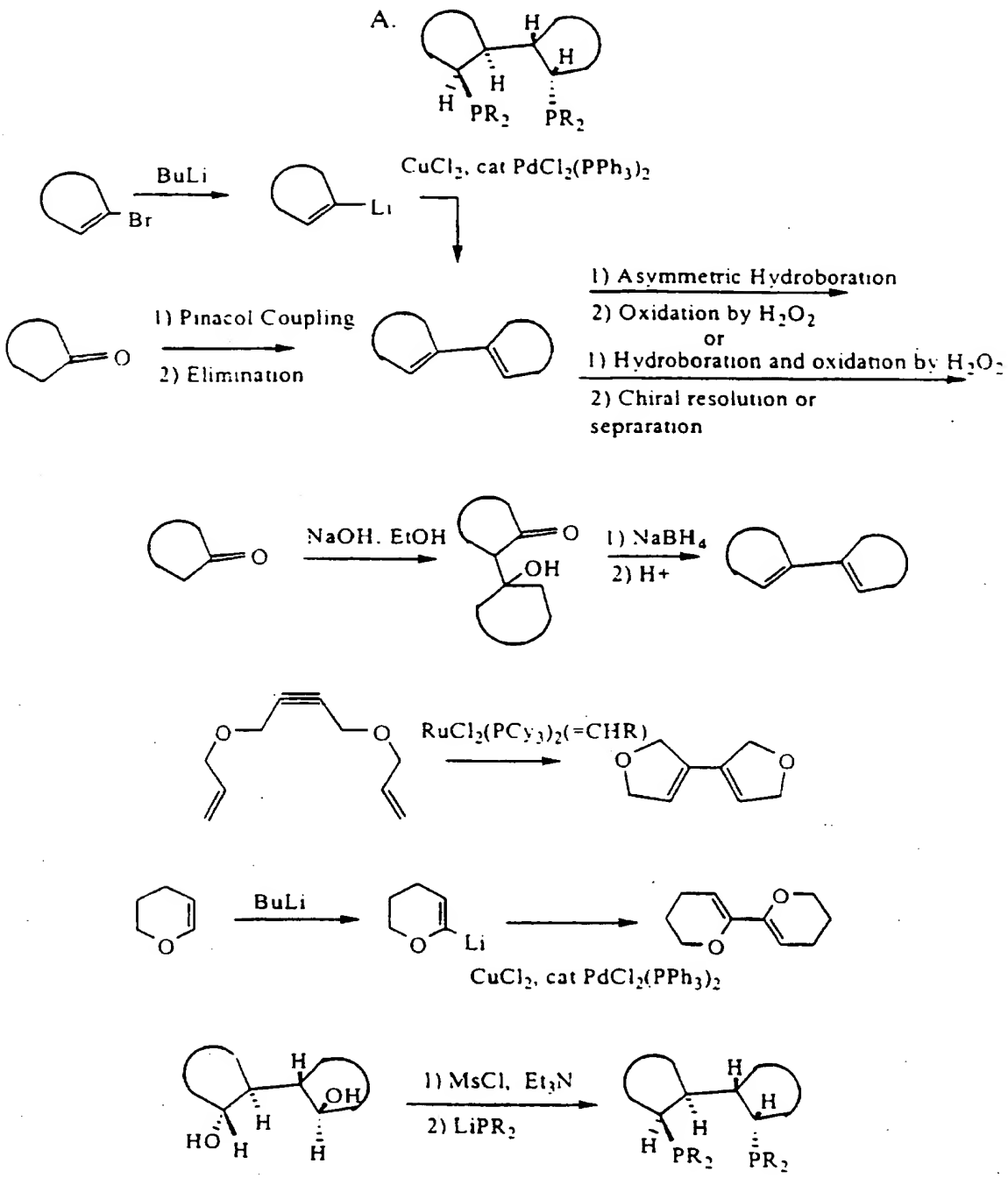

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FIGURE 8B

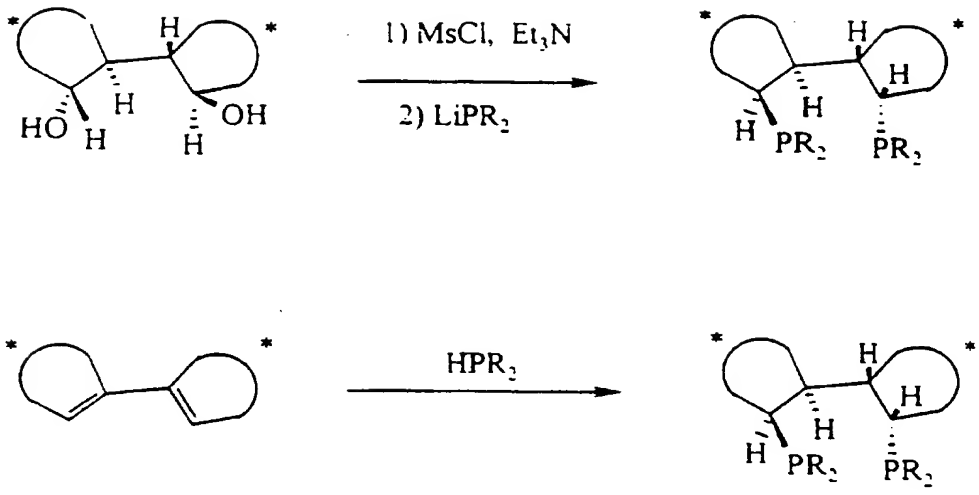

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FIGURE 8C

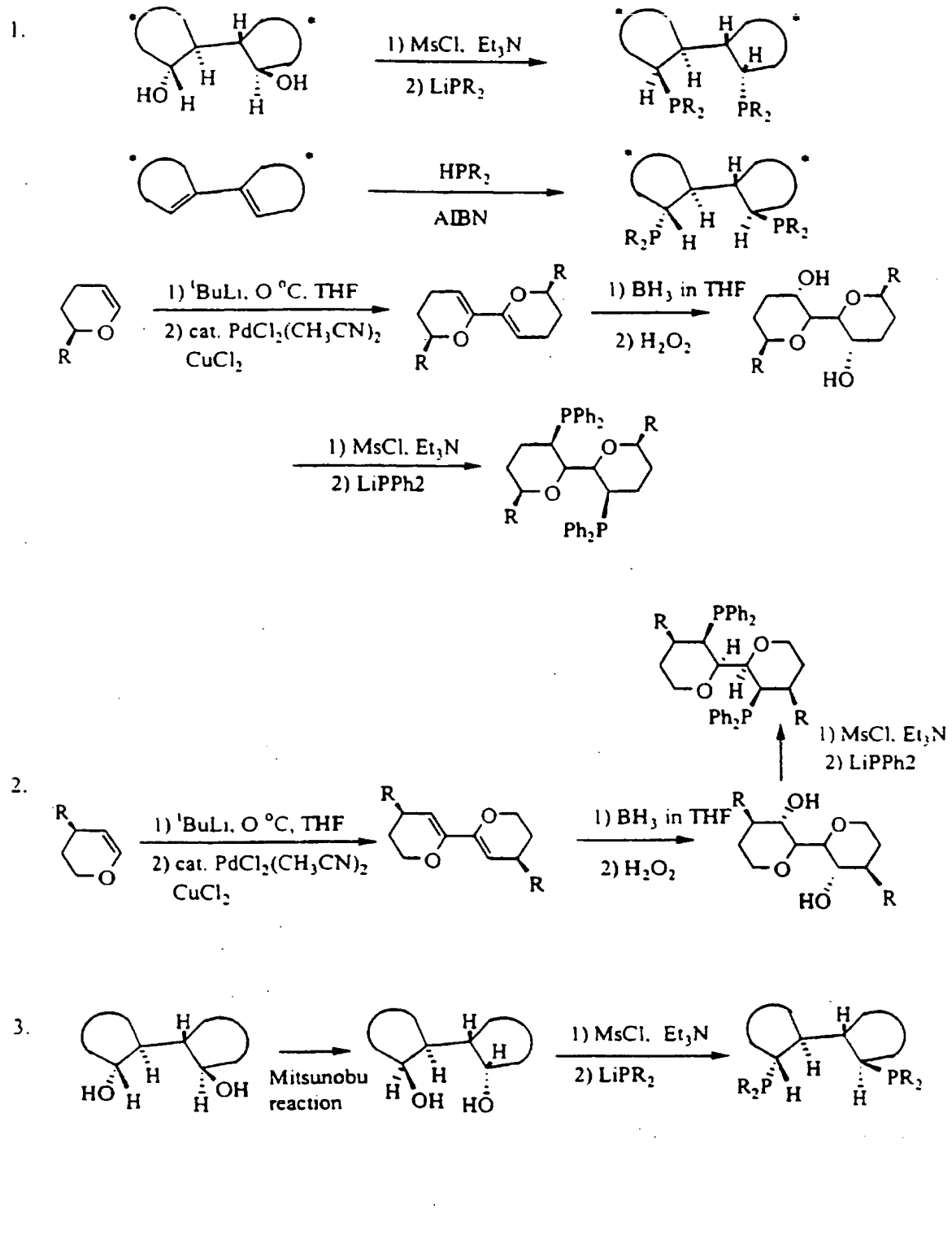

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FIGURE 9

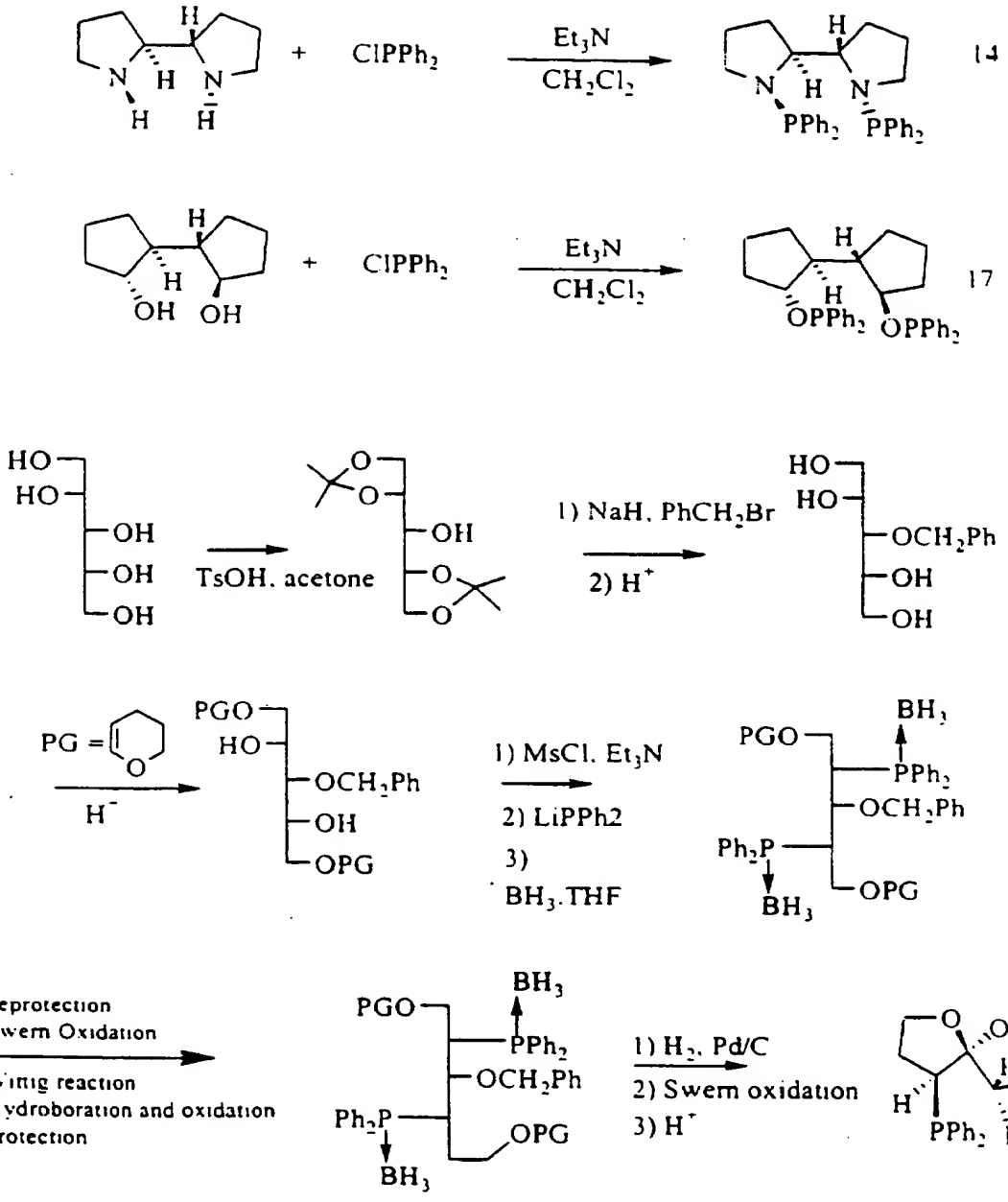

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FIGURE 10

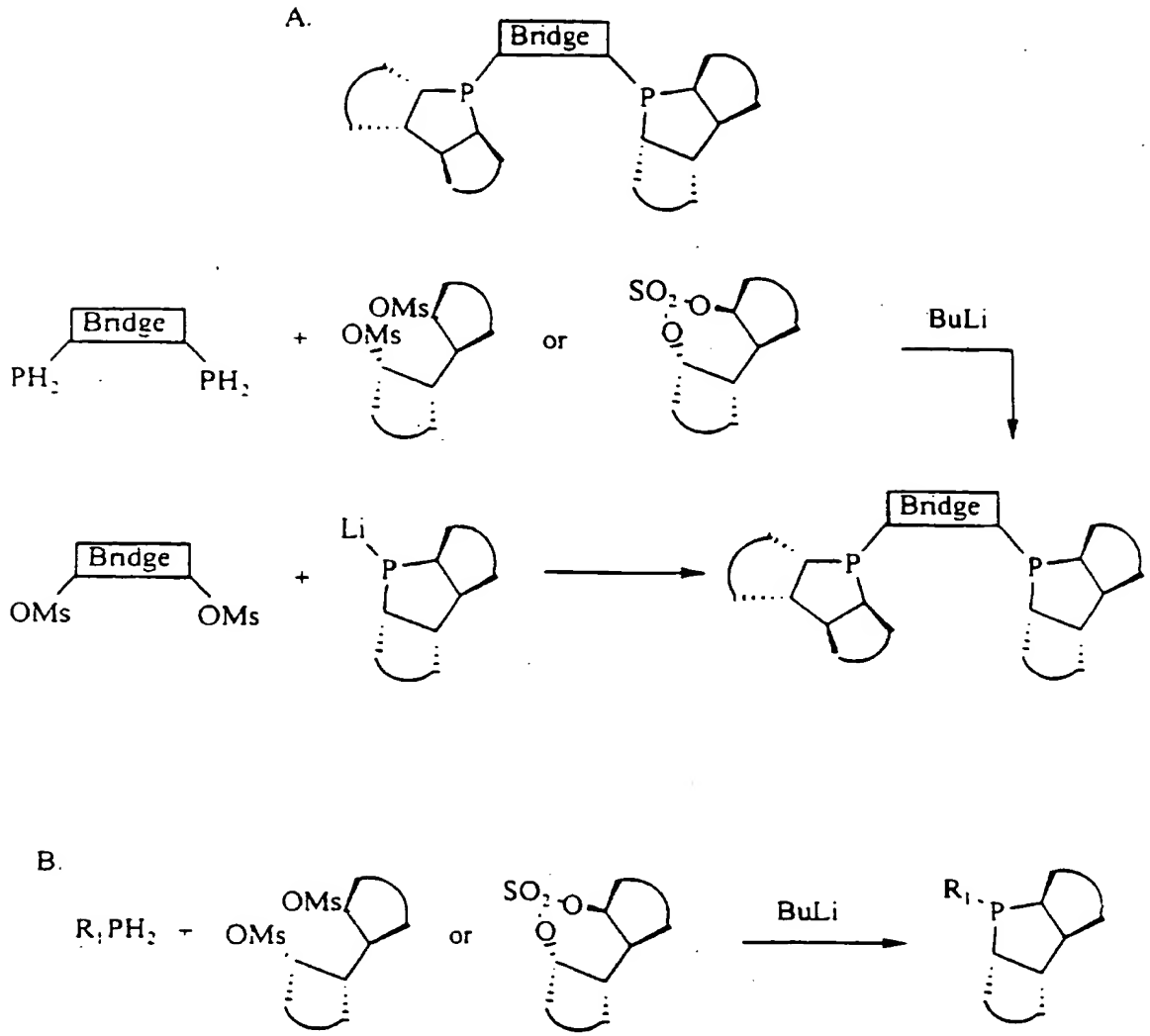

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FIGURE 11

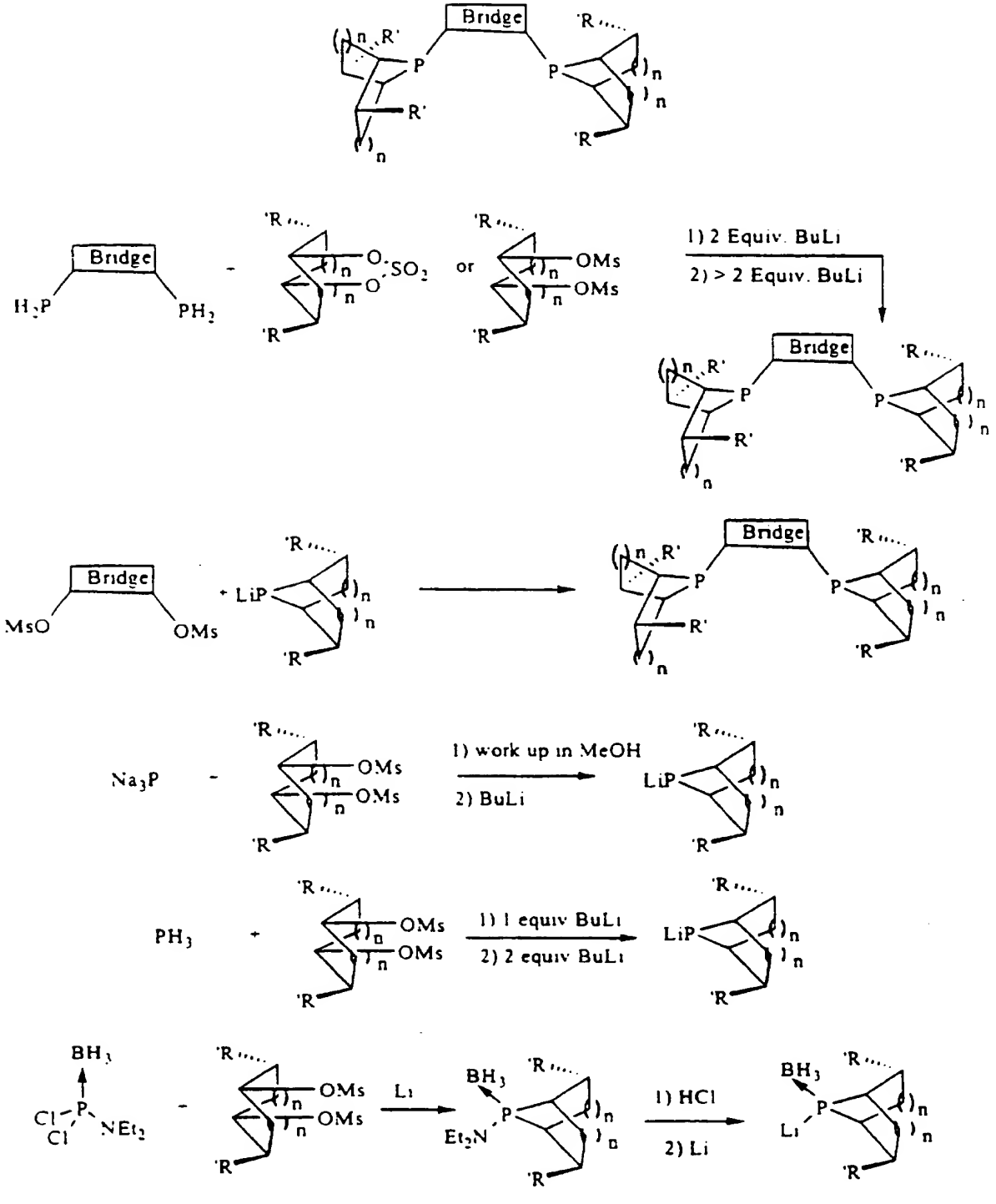

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FIGURE 12

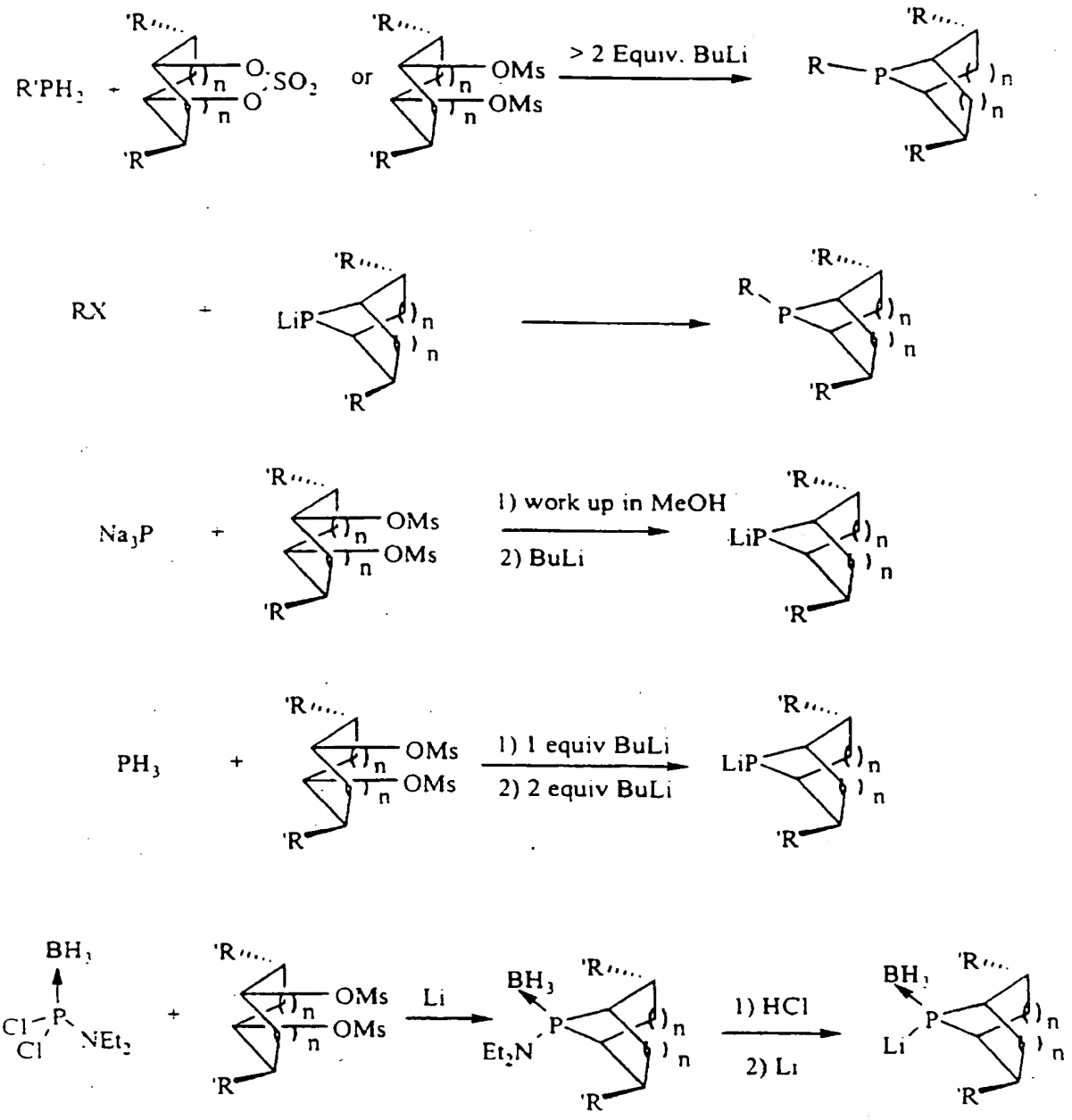

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FIGURE 13

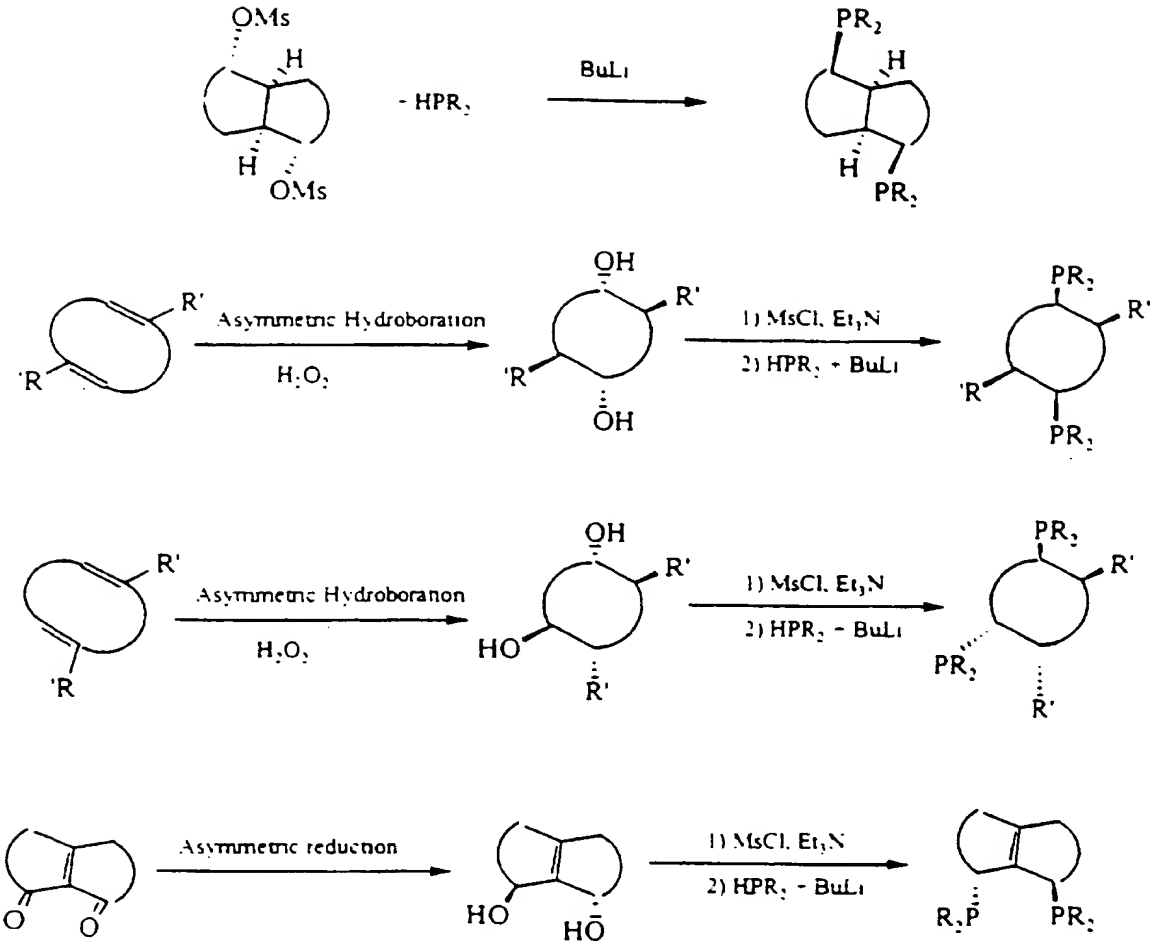

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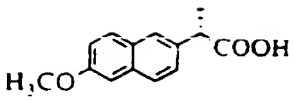
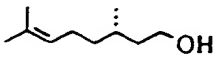
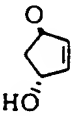
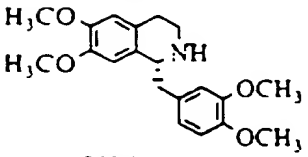
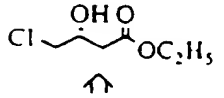
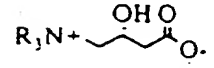
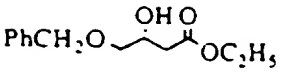
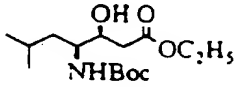
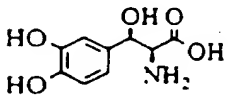
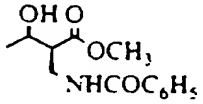
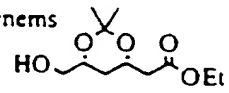
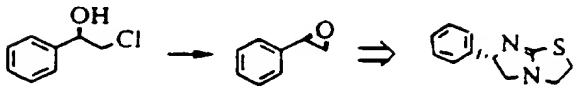
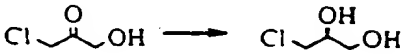
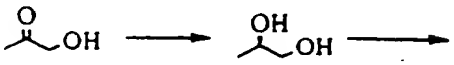
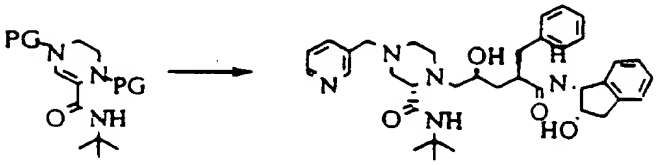
FIGURE 14

	Naproxen	Antiinflammatory Agent
	(S)-Citronellol	Fragrance
	Intermediate	Synthesis of Prostanglandins
	Enamide hydrogenation	Synthesis of isoquinoline alkaloids, Morphine, Benzomorphans, Dextromorphans
	R = CH_3 Carnitine	Transport of long-chain fatty acids through membranes
	R = H GABOB	Anti-epilepic and hypotensive drug
	Intermediate	Compactin, a human menopausal gonadotropin-coenzyme A redutase inhibitor
	a protected statine	aspartic proteinase inhibitor
	L-DOPS	an anti-Parkinsonian agent
	Intermediate	Antibiotic carbapenems 
		Levamisole
		Daiso Technology
		Levofloxacin
		HIV Protease Inhibitor Merck - Indinavir

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US97/10436

A. CLASSIFICATION OF SUBJECT MATTER
IPC(6) :C07F 9/50, 9/28; C07D 331/02, 331/04, 333/46
US CL : 568/12, 14, 17; 546/21, 24; 549/5, 9, 13, 216
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
U.S. : 568/12, 14, 17; 546/21, 24; 549/5, 9, 13, 216

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
Please See Extra Sheet.

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	CHEN et al. Synthesis of Novel Chiral 2,5-Dialkyl-7-phosphabicyclo[2.2.1]heptanes, and Their Application in Highly Enantioselective Pd-Catalyzed Allylic Alkylations. J. Org. Chem. June 1997, Vol. 62, pages 4521-4523, see entire document.	1, 13-15, 18-20, 24-25, 28

[X] Further documents are listed in the continuation of Box C. [ ] See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search 03 OCTOBER 1997	Date of mailing of the international search report 28 OCT 1997
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer JEAN F. VOLLANO Telephone No. (703) 308-1235

Form PCT/ISA/210 (second sheet)(July 1992)*

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US97/10436

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	Database Casplus on STN, Chemical Abstractsm(Columbus Ohio, USA), GELLING,O.J. 'Preparation of acetals by catalytic hydroformylation of alkenes,' abstract, WO9506025, March 1995, see entire document.	1, 16,18
A	OKADA et al. The First Synthesis of Chiral Phosphinocarboxylic AcidLigands,Trans-2-(Diphenylphosphino) Cycloalkanecarboxylic Acids. The Phosphine-Palladium Complexes Catalyzed Asymmetric Allylic Alkylation.Tetra. Lett. July 1990, Vol.31, No.27, pages 3905-3908.	1, 7-10, 13-18
A, P	US 5,596,114 A (BURK) 21 January 1997.	1, 7-10, 13-18
A	US 5,258,553 A (BURK) 02 November 1993.	1, 7-10, 13-18
A	US 5,426,223 A (BURK) 20 June 1995.	1, 7-10, 13-18
A	US 5,177,230 A (BURK) 05 January 1993.	1, 7-10, 13-18
A	US 5,008,457 A (BURK) 16 April 1991.	1, 7-10, 13-18
A	US 3,105,096 A (WELCHER) 24 September 1963.	1, 7-10, 13-18

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US97/10436

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.: 2-8 AND 11-12
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

The claims recite the limitation of "D" as a ring structure however the figures in the claims do not have a D drawn within them.

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☒ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☒ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US97/10436

B. FIELDS SEARCHED
Electronic data bases consulted (Name of data base and where practicable terms used):

APS, CAS ONLINE, BEILSTEIN, GMELIN
search terms: hydroformylation, phosphine, phosphinite, catalyst, chiral, bridged phosphines, platinum group metals, Diels Alder, hydrocarboxylation, Heck reaction, rhodium phosphines, platinum phosphines, also did structure drawning search on each different intermediate group.